

RENAL HYPERTENSION

By

EDUARDO BRAUN-MENÉNDEZ
JUAN CARLOS FASCIOLO
LUIS F LELOIR
JUAN M. MUÑOZ
ALBERTO C TAQUINI

Institute of Physiology, Faculty of Medical Sciences
and
Institute of Cardiology, V F Grego Foundation
Buenos Aires, Argentina

Translated by

LEWIS DEXTER, M.D

Harvard Medical School and Peter Bent Brigham Hospital,
Boston, Massachusetts



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PROLOGUE

Recent advances in our knowledge of renal hypertension represent an outstanding accomplishment in experimental medicine An insight has been given into its pathology, an important field of investigation has been opened, and the hope of being able to prevent and cure one of the gravest of human diseases has been renewed.

The first real knowledge concerning renal hypertension began with Bright's accurate observation that hypertrophy of the heart frequently accompanies diseases of the kidneys. Later, on discovering methods of measuring arterial blood pressure, it was easy to demonstrate that such diseases were associated with hypertension and that the cardiac hypertrophy was a consequence of the hypertension.

No new important advances were made in our knowledge of the rôle of the kidney until Tigerstedt and Bergman demonstrated, in 1898, that extracts of the kidney possess a hypertensive action. They gave the name, renin, to the impure substance which produced this effect.

In that period the vasoconstrictor action of extracts of three organs had been demonstrated: the adrenal medulla, the hypophysis, and the kidney.

The discovery of adrenalin led to the hypothesis that its hypersecretion was the cause of hypertension. The adrenal theory, or more exactly that of hyperadrenalism, was formulated almost immediately after its discovery, first by Josué, and subsequently by many other clinicians This theory transferred interest from the kidney to the adrenal medulla.

Much credit is due the indefatigable investigations of Volhard who was convinced that a vasospastic factor existed in the so-called pale hypertension, as was indicated by ocular and cerebral symptoms and by blanching of the vessels of the skin. Since he believed that the exaggerated contraction of these vessels was due to a substance circulating in plasma, he devoted himself with the help of his students to a search for its presence He first showed the impossibility of demonstrating the presence of an excess of adrenalin in the circulating blood, although later some of his students, such as Bohn (1931), described the presence of specific vasoconstrictor substances in the

blood of hypertensives This was subsequently disproven by numerous investigators

In our Institute, plans for the study of this problem began when we had the misfortune of losing Juan Guglielmetti, in 1923, who died of malignant hypertension at the age of 33. Among those who have worked with us, he ranks as one of the most capable and talented. An attempt was made to produce experimental hypertension of renal origin in dogs by subtotal nephrectomy with limited success (Biasotti, 1927) New attempts were made by constricting the renal vein, but the hypertension was inconstant and transient (Braun-Menéndez, 1932).

Shortly after the discovery that permanent hypertension might be produced by section of the four pressor receptor nerves, attention was directed toward nervous factors which for some time had been considered as possible causes of arterial hypertension.

The modern period is due entirely to Goldblatt who, in 1932, and in a classical report of 1934, gave investigators an easy and sure method of producing permanent hypertension of renal origin. This procedure simply consists of reducing the diameter of the renal artery, and is referred to, with dubious correctness, as producing a partial ischemia or incomplete ischemia, which are terms now established by usage In the skilled hands of this trained investigator and with the contributions of many other investigators from different countries, it was shown that this hypertension was not due to a nervous mechanism such as a reflex of renal origin or hyper-reactivity of the vasoconstrictor nerves New investigations were carried out principally in the United States, Belgium, Argentina, and England.

In 1936, we renewed our studies with Fasciolo who energetically overcame innumerable initial difficulties After confirming previous studies we

kidney of a

a hypertensive substance which today we know as renin This was demonstrated by grafting a kidney by vascular anastomosis of its artery to the carotid and of its vein to the jugular into the neck of a dog recently nephrectomized The following year, with Taquini, we showed that the citrated plasma of venous blood of an ischemic kidney contained a vasconstrictor substance which did not exist in the plasma of normal venous blood

At that point the subject passed into the hands of a team of investigators at the Institute of Physiology, whose combined efforts led to important discoveries This group consisted of E Braun-Menéndez, J C. Fasciolo, L. F Leloir, J. M Muñoz, and A. C Taquini, while important contributions over shorter periods of time were made by J W Bean, R. Dell'Oro, L Dexter, V G. Foglia, M. Gaudino, F Huidobro, F P. Ludueña, and J. M Moglia.

In 1939, an important discovery was made almost simultaneously in Argentina and in the United States. Braun-Menéndez, Fasciolo, Leloir and Muñoz extracted a substance which they called hypertensin from the venous blood of ischemic kidneys, which was produced by the action of renin on a plasma globulin called hypertensinogen or precursor of hypertensin They showed that this same hypertensin was produced by incubating renin with hypertensinogen *in vitro* It was demonstrated, furthermore, that the kidney secreted renin which, though not of itself vasoconstrictor, rapidly produced the vasoconstrictor substance, hypertensin, upon coming in contact with the hypertensinogen of plasma Evidence was presented that the reaction was enzymatic in nature

Attacking the problem from a different angle, Page and his collaborators reached similar conclusions. They showed that renin did not possess a vasoconstrictor action when it was perfused in saline solution through an isolated surviving vascular system When serum or plasma was added, vasoconstrictor properties appeared. They at first believed that the plasma contained an activator of renin but later showed that the appearance of the vasoconstrictor action was due to the formation of a new substance which they called angiotonin Unfortunately, the numerous publications of Page and his school, although making important contributions and advances, included many assertions not always well demonstrated, affirmed the existence of many substances which are doubtful, and formulated numerous hypotheses and concepts which were not always in accord Fortunately, their conclusions have gradually become similar to our own Today the principal discrepancy is one of terminology All agree that renin through its action on a plasma globulin (hypertensinogen, renin activator, renin-substrate or prehypertensin) produces a vasoconstrictor substance (hypertensin or angiotonin)

In the clinic, the existence of hypertension from renal ischemia

similar to experimental renal hypertension, has not only been demonstrated but the hypertension has been cured by removal of the diseased kidney in some cases of unilateral renal disease. There are no definite proofs, however, that all hypertensions have a renal origin Nervous factors appear to participate in variable degree in the genesis and maintenance of human hypertension.

Finally, endocrine and other metabolic factors are recognized as playing a rôle in certain instances Whatever may be the respective importance of these various factors and whatever may be the course of future investigation, there is no doubt but that experimental studies on renal hypertension have strongly influenced current ideas and have stimulated numerous investigations These have furthermore been facilitated by recent outstanding advances in the physiology of the kidney and in the development of renal function techniques It is important, however, to recognize clearly the obscure and badly demonstrated points in order to undertake new investigations.

Although numerous medical and surgical therapeutic attempts have given variable results and as yet can not be considered to be satisfactory, we have the advantage of new knowledge which allows us to test experimentally the action of various therapeutic agents on renal or neurogenic hypertension in animals before testing them on man We should not be alarmed if it takes considerable time to attain success since advances are always slow in biology. It only suffices to recall that thirty-three years elapsed between the demonstration of experimental pancreatic diabetes and the discovery of insulin

The secretion of renin is one more example of a homeostatic substance produced by the organism It is a true internal secretion which does not exist or is only of slight importance under normal conditions In the presence of severe hypotension, it constitutes one of the numerous mechanisms at the disposal of the body for aiding in the recuperation of blood pressure. Under pathologic conditions of renal ischemia this secretion unfortunately acquires a hypertensive character.

A regulatory mechanism of blood pressure has thus been discovered, and has been clearly demonstrated in birds and mammals. Since it appears only in pathologic conditions which affect the

kidney, it is presumably an advantageous mechanism. It is easy to postulate, for example, the attractive but uncertain teleologic hypothesis that the hypertension thus produced is useful in increasing the renal blood flow or the glomerular filtration.

A curious fact is that the action of renin is indirect. Itself inert, it acts upon the hypertensinogen of plasma to produce the constrictor substance, hypertensin, whose action is ephemeral since it is rapidly destroyed in the body.

This monograph is a study of renal hypertension only and summarizes the present state of our knowledge. The enormous amount of work done on this subject is reflected by an abundant literature. Conclusions have sometimes been contradictory and sometimes excessive. The authors have an extensive firsthand experience which permits them to describe their own valuable contributions and to discuss the problem in critical fashion. This book, in addition to its original contribution wherein lies its true value, constitutes at the present time the most important source of information on the subject. I think that its reading will not only be instructive but will suggest new ideas and new subjects of study and investigation. An appendix describes the methods which have not as yet been published in detail. It is hoped that it will facilitate the work of future investigations.

B. A. Houssay

INTRODUCTION

Study of hypertension has experienced a remarkable impetus in recent years thanks to the efforts of both physiologists and clinicians. It has at times been considered by those unfamiliar with research that investigations by clinicians and by physiologists have no common ground Both are actually sources of mutual information which help in the interpretation and discovery of natural phenomena Evolution in our knowledge of arterial hypertension is a clear-cut example of this The clinical pathologic approach led to the discovery of the rôle of the kidney in hypertension, and the physiologic approach to the reproduction of this disease and to the study of its pathogenesis. Knowledge acquired experimentally made it possible for the clinician to discover new renal disorders capable of producing hypertension which had passed unnoticed until that time, and to develop methods of unquestioned value for the investigation of the function of the kidney.

As Professor Houssay stated in the prologue, the subject of renal hypertension has been intensively studied at the Institute of Physiology of the Faculty of Medical Sciences of Buenos Aires. Investigations performed up to the year 1938 had demonstrated that the ischemic kidney of a hypertensive dog liberated a pressor and vasoconstrictor substance into the blood stream At the end of that year, at the suggestion of Professor Houssay, we joined forces with the object of isolating this substance Such collaboration is a necessity in modern investigation when one aspires to solve a problem of considerable magnitude The use of many available resources demands the distribution of responsibility and the help of specialists.

We have worked together for five years, each one contributing his measure in a common effort to elucidate the problem of hypertension which is so deleterious to the health of mankind and for which there is so great a need of solution. We have depended on other colleagues for their help, knowledge and ingenuity We have counted above all on the inspiration, stimulus, and disinterested help of our teacher, Professor Houssay The Institute of Cardiology, Foundation, V. F. Grego, which one of us (A C T) directs, was founded in 1941. As members of this and as guests of the Institute of Physiology, two

of us (A.C.T. and J.C F) have worked for the last two years. May we express our deep appreciation to the members of each institution.

We have believed that it would be useful at this stage of our efforts to unite in writing a monograph concerning our present knowledge of renal hypertension Several excellent articles on this subject have been written by investigators with wide personal experience,[1] but these articles by their nature have not been able to embrace the subject in all its ramifications. Our main purpose has been to explain as clearly as possible the present status of the problem, mentioning what is definitely known, indicating the gaps in our knowledge, and pointing out new lines of attack. Since our own endeavors have been mainly concerned with experimental renal hypertension, we have given particular attention to this aspect of the subject.

Although it has not been shown that human hypertension is due to the same mechanism as that produced by experimental renal ischemia, considerable evidence exists to suggest that the mechanism of each is closely related. Although our personal contribution in respect to human hypertension is limited, we have felt that it is necessary to discuss the *pros* and *cons* of the rôle of the kidney in human hypertension and to point out the similarities and differences which exist between human and experimental renal hypertension. Only incidentally will we refer to other aspects of the wide field of human hypertension which have been well analyzed in several pathological monographs

We have endeavored to make our bibliography complete. Since causes of error in biologic investigation are numerous and may well escape even a careful critique, we have in each case cited the authors on whose shoulders falls the responsibility of a given statement. The reported results have at times been contradictory. In our interpretation, we have depended mainly upon the scientific accuracy of the investigation In addition, however, we have taken into account the authority of the investigator presenting a given statement as judged by the calibre, integrity, and critique of his writings.

Finally, we wish to explain certain features of this book. Since

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some of the fundamental concepts may not be sufficiently clear to the reader due to the abundance of bibliographical data, we have written a résumé at the end of each chapter for those who are not familiar with the subject. In the appendix, some of the techniques which we have devised are described. These we have used in the majority of our experiments Our object in describing them here is to facilitate confirmation and continuation of our work by other investigators.

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TRANSLATOR'S PREFACE

It has been a little more than a decade since the discovery of a satisfactory method for the experimental production of renal hypertension in animals. During this period, an enormous amount of investigation has been performed and rapid strides in the understanding of this disorder made. Although much remains to be accomplished both in the experimental and in clinical fields, it is appropriate that a summary of the work performed to date should appear at this time not only to describe what has been accomplished but to point out the gaps in our present knowledge.

The authors are particularly qualified to do this. Their members represent the physiological, chemical, and clinical fields working together in the laboratory of Professor Bernardo A. Houssay. Their method of presentation consists of critically reviewing practically all pertinent literature concerned with renal hypertension and of offering their interpretation in the light of available evidence. In any field as controversial as this, the reader may well disagree with the authors' interpretation since many problems, as they point out, are unsettled. The reader has the advantage, however, of becoming acquainted with the views of those who have perhaps been responsible more than any other group for the clarification of the renal humoral pressor mechanism.

The first edition of this book was published in 1943. Advances made since then have been incorporated in this English edition. The translator has not attempted to produce a line for line translation but has tried to present a version which would convey the authors' views to readers in this country. In difficult passages he has been aided by Dr. Luis F. Leloir and Dr. Juan Reforzo-Membrives. Preparation of the illustrations for reproduction was performed by Mr. James Ufford of the Photographic Department of the Fogg Art Museum. In preparing the manuscript and illustrations, the translator is indebted to Dr. Florence W. Haynes, Mrs. Wiley F. Barker, Miss Ann Fitz-Gibbon, and to his wife. He especially wishes to express his thanks to Miss Frances J. Cushman for her untiring effort in typing and checking the manuscript.

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LEWIS DEXTER

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Peter Bent Brigham Hospital

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RENAL HYPERTENSION



CHAPTER I

PRODUCTION OF PERMANENT HYPERTENSION

For many years attempts were made to produce permanent hypertension in laboratory animals with the object of systematically studying the factors concerned in its production

The majority of attempts were performed on the kidney due to the fact that it was repeatedly suspected to be the organ responsible for hypertension in man. Before the investigations of Goldblatt, however, attempts were unsuccessful because either hypertension in the animal could not be produced or the elevation obtained was slight, transient, or reproducible with difficulty Certain investigators, on the other hand, demonstrated the possibility of producing hypertension without the participation of the kidney, which tended to wrest away from this organ its importance as a cause for the disease

In the year 1934, Goldblatt, Lynch, Hanzal and Summerville made a brilliant discovery by showing that reduction in the amount of blood brought to the kidney gave rise to permanent hypertension in the dog This discovery changed the orientation of investigations on hypertension. The simple and reliable technique of Goldblatt and his collaborators allowed a methodical study of the problem to be made

In this chapter the various procedures employed for obtaining prolonged hypertension of renal origin will be described Procedures will also be mentioned which do not act directly through the kidney As will be seen later, however, there is evidence that the kidney plays a rôle in the production of all these types of hypertension

Before examining the results obtained with different procedures, the possible causes for contradictory results obtained by different authors in their use of a given procedure should be pointed out These discrepancies can in part be explained by (a) different species of animals employed, (b) individual variations in operative techniques, (c) different periods of observation to which the animals were submitted; (d) elevation of blood pressure considered sig-

nificant; and (e) methods employed for the determination of blood pressure.

The technique used in recording blood pressure is of fundamental importance in evaluating the results obtained by different authors In the dog, arterial puncture is an excellent method as long as the animals are maintained perfectly quiet during the determination. Indirect methods are less reliable with the exception of the method of Van Leersum (1911). Kernodle, Hill, and Grimson (1944) have recently described a method of recording blood pressure in dogs during activity, rest, and natural sleep This consists of suturing cuffs enclosing a rubber balloon around femoral and iliac arteries and connecting them with a suitable recording manometer. Although no comparison with direct blood pressure readings was described, this is the only method at this time for obtaining blood pressure under conditions of sleep and activity in dogs.

In the rat, the plethysmographic method of Williams, Harrison and Grollman (1939) gives results which are satisfactory although when compared with readings obtained by direct arterial puncture and recorded with a Hamilton manometer, Shuler, Kupperman and Hamilton (1944) found the true pressure to average 40 ± 10.7 mm. Hg higher than that recorded by the tail method with tail cuffs 26 to 40 mm wide as are usually advocated. Much greater accuracy was obtained with 5 mm. cuffs.

In small animals, such as the rat, rabbit, and so forth, general anesthesia and subjective méthods for the recording of blood pressure have been devised. Results obtained by these techniques are not entirely reliable.

Many details of the various procedures for recording arterial blood pressure in animals can be found in the monograph by Fasciolo (1939).

NEUROGENIC HYPERTENSION BY SECTION OF THE PRESSOR REGULATOR NERVES

Arterial pressure is regulated by reflex pathways through pressor receptor mechanisms located principally in the carotid and aortic sinuses For a description of these mechanisms, we refer the reader to the excellent monograph of Heymans, Bouckaert and Regniers (1933). A schema of the principal circulatory reflexes is shown in figure 1.

Hering, in the year 1927, showed that removal of the pressor regulator system—aortic and carotid sinus nerves—produced acute hypertension in several species of animal, especially in the rabbit. His attempts to obtain chronic hypertension were not entirely successful. His disciples, Koch and Mies (1929), however, obtained rises of blood pressure in rabbits lasting many months Koch, in 1931, obtained hypertension which lasted several months in the dog as a

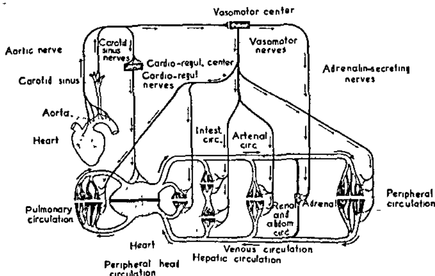


FIGURE 1 DIAGRAMMATIC REPRESENTATION OF THE MAIN PHYSIOLOGIC FUNCTIONS OF THE PRESSO-SENSITIVE REFLEXOGENIC VASCULAR AREAS IN THE HOMEOSTASIS OF CIRCULATION

(After Heymans, New England J Med, 1938, *219*, 147)

result of resection of the carotid sinus and of the depressor nerves Similar results were obtained in the same year by Heymans and Bouckaert (1931) Further confirmation has been offered by Kremer, Wright and Scarff (1933) and Introzzi, Amici di San Leo and Rosito (1938) in rabbits, and Dautrebande (1932), Nowak (1940), Grimson (1940), Thomas (1944) and Bing (1944) in dogs Persistence of the hypertension by this method has not, however, been observed in all cases Koch and Mattonet (1934) were unable to obtain chronic hypertension Green, De Groat and McDonald (1935) observed only

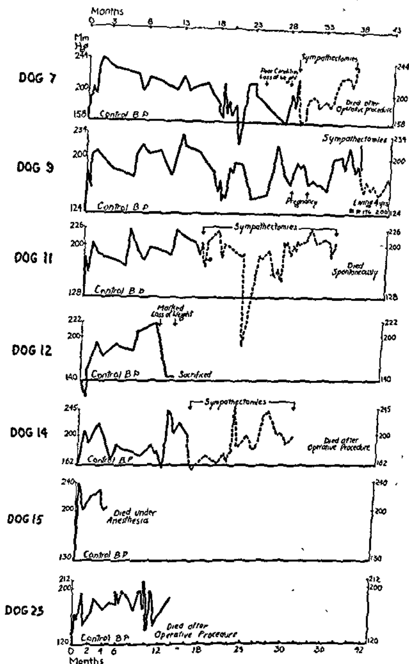


FIGURE 2. HYPERTENSION FROM SECTION OF DEPRESSOR NERVES

Blood pressures in dogs with chronic hypertension produced by carotid sinus and aortic-depressor denervation Note the persistence of hypertension produced by this procedure (After Nowak, Ann Surg., 1940, *111*, 102 By permission of J. B Lippincott Company).

transient hypertension in the rabbit, and irregular or slight hypertension in the dog Introzzi (1939) found that the pressure tended to fall with the passage of time, although he obtained hypertension which lasted for 110 days in 21 rabbits Goldblatt, Kahn, Bayless and Simon (1940) were likewise unable to obtain persistent hypertension in dogs

Despite these results, the hypertension obtained may be permanent, lasting for at least two years after operation according to Heymans and his collaborators These results have been confirmed by Nowak (1940), Grimson (1940), and Thomas and Warthin (1940). Heymans and his collaborators believe that difficulties encountered in obtaining permanent hypertension are attributable to the technique employed They recognize that in a certain number of animals the rise obtained can be transient, which they explain by the presence of accessory nerve fibers or by the vicarious action of other pressor receptor zones Nowak (1940) carried out a careful study of this problem and produced hypertension which persisted as long as three years and four months in ten dogs in which he resected the bifurcation of both carotids and extirpated the depressor nerves of the neck (figure 2). In four dogs chronic hypertension was not obtained; in two of these there were signs of cardiodepressor activity Thomas (1944) has observed pressures as high as 425 mm Hg systolic and 222 mm Hg diastolic and hypertension lasting for at least five years in dogs with neurogenic hypertension.

CHARACTERISTICS OF HYPERTENSION BY SECTION OF THE PRESSOR REGULATOR NERVES A hypertension of 250 mm Hg or more may follow section of the pressor regulator nerves, and becomes rapidly established after the operation Nowak (1940) and Thomas (1944) observed rises within two days, but in general the blood pressure became definitely elevated two or three weeks later Tachycardia is at times pronounced and bears a relation to the degree of hypertension (Thomas, 1944, Bing, 1944)

Another characteristic of this type of hypertension is the fluctuation of the blood pressure Lambert and Wakerlin (1944) have recently emphasized this point Goldblatt (personal communication, 1945) has observed marked fluctuations of blood pressure in dogs with this type of neurogenic hypertension, the pressure rising to great heights under conditions of excitement and falling to essentially normal levels when the dogs are quiet and at rest Grimson

Kernodle and Hill (1944) found blood pressure and pulse to be markedly reduced during sleep in dogs with neurogenic hypertension and to be elevated during activity. The response to several sedatives and anesthetics was variable. At times, prolonged remissions have been observed, although in some cases these have been attributed to some intercurrent process; in others no satisfactory explanation has been found (Nowak, 1940).

The degree of hypertension reached in these animals depends principally on the vasomotor tone of the sympathetic nervous system Bacq, Brouha and Heymans (1934) and Heymans and Bouckaert (1935, 1936) showed that total bilateral gangliar sympathectomy, from the cervical ganglion to the pelvic chain, cured or prevented the hypertension produced by section of the pressor regulator nerves The studies of Grimson (1940) and Nowak and Walker (1939) indicated that such an operation performed previously did not prevent a slight rise of pressure in all cases. Schafer (1942) observed that paravertebral sympathectomy caused a reduction of the blood pressure in these animals, and if the sympathectomy was carried out previous to section of the pressor regulator nerves, only a slight elevation of blood pressure took place. More recently, Schafer (1944) found that the blood pressure of four dogs with neurogenic hypertension fell markedly as a result of the administration of 2,5-dimethyl paraquinone (xyloquinone) whereas the blood pressure of three normal dogs remained unchanged.

Figure 3 demonstrates the effect of section of the pressor regulator nerves in a normal and in a totally sympathectomized animal, and in figure 4 the effect of sympathectomy on the blood pressure of dogs with neurogenic hypertension is shown.

Extirpation of the thoracic sympathetic nerves in animals with neurogenic hypertension causes the pulse rate to return to normal but the blood pressure remains elevated (Heymans and Bouckaert, 1935)

Nordmann (1929), Introzzi (1939) and Gorev and Budnitzka (1940) demonstrated the existence of cardiac hypertrophy in rabbits and dogs made hypertensive by section of the pressor regulator nerves Leriche, Fontaine and Froehlich (1936), and Fontaine and Mandel (1938a, b) showed that it is possible to remove one and a half adrenal glands in these animals without modifying the hypertension.

Schafer (1942) studied the blood volume in this type of hypertension After section of the pressor regulator nerves, the red cell volume increased without change of plasma volume. Gangliar sympathectomy diminished the blood pressure and brought the blood

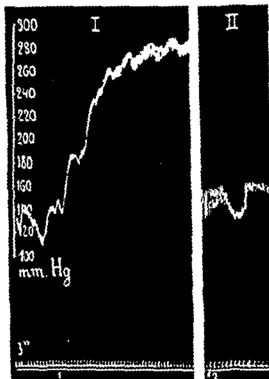


FIGURE 3, EFFECT OF SECTION OF THE DEPRESSOR NERVES IN SYMPATHECTOMIZED ANIMALS

4, 487).

volume back to normal After sectioning the pressor receptor nerves in sympathectomized animals, a slight rise of blood pressure appeared while the blood volume remained unchanged

Nowak (1910) did not observe changes in red cell volume or in the number of red cells circulating in the blood of these animals

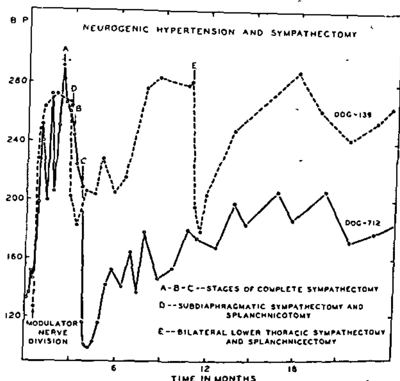


Figure 4 Effect of Sympathectomy on the Blood Pressure of Dogs with Neurogenic Hypertension

This hypertension was produced by division of the modulator nerves Total paravertebral sympathectomy was performed on dog 712 in three stages, A, B, and C Bilateral subdiaphragmatic splanchnicotomy and lumbar sympathectomy (D) and later bilateral lower thoracic sympathectomy and splanchnicectomy (E) were performed on dog 139 Some restoration of hypertension occurred after each procedure The complete sympathectomy effected a more pronounced lowering of the blood pressure than the partial sympathectomies The restoration of the blood pressure after the total sympathectomy was incomplete (After Grimson, Internat Abstr Surg, 1942, 75, 421 in Surg Gynec & Obst, 1942 By permission of Surgery, Gynecology, and Obstetrics)

No significant changes were found in the concentration of sugar, fat, protein, chloride, calcium, oxygen and carbon dioxide content of the blood

Bing (1944) found that as this type of hypertension developed in dogs, heart rate and cardiac output increased while the systolic discharge remained constant. Renal blood flow and the filtration rate, as measured by clearance techniques, showed no significant change,

but blood flow through the limb, measured plethysmographically, increased in every instance. Total peripheral resistance rose slightly in two animals and remained constant in the remaining four. Renal resistance increased more than 50 per cent while vascular resistance in the forelimb fell It was concluded that neurogenic hypertension is accompanied by a rise in cardiac output, constriction of the renal afferent arterioles, and an accelerated circulation in the extremities indicative of increased sympathetic tone Thomas and McLean (1944) found that the pressor action of epinephrin and hypertensin were not significantly altered in unanesthetized dogs by the induction of neurogenic hypertension Hypertensin accelerated the heart rate in these dogs while the rate was slowed in dogs without neurogenic hypertension

HUMORAL FACTORS Humoral factors appear to play a certain rôle in this type of neurogenic hypertension Hartwich and Hessel (1931), and Konschegg (1935) demonstrated vasoconstrictor substances in the blood of rabbits made hypertensive by section of the pressor receptor nerves Similar results were obtained later in dogs by Heymans and Bouckaert (1938) Hermann and Delrieu (1939) and Hermann, Jourdan and Delrieu (1939b), using the Lawen-Trendelenburg preparation, noted a vasoconstrictor action of the serum of hypertensive dogs The participation of adrenalin or sympathin in this type of hypertension has received certain support from the experiments of Jourdan and Galy (1939) and Heymans and Bouckaert (1933) who showed that the injection of such sympathicolytic substances as Fourneau 933 or ergotamine into dogs with neurogenic hypertension produced a distinct fall of blood pressure. The constrictor action of the serum could not be attributed entirely to adrenalin, however, because Hermann, Jourdan and Delrieu (1939a) found that it persisted after denervation or removal of the adrenal capsules These investigators believed that sympathin might be responsible The vasconconstrictor action of the serum of animals with this type of hypertension must be accepted with reservation since Taquini (1938b), using the Lawen-Trendelenburg preparation, did not observe any vasoconstrictor action of the arterial blood of dogs recently subjected to denervation of the pressor receptor nerves

RENAL FACTORS Grimson, Bouckaert and Heymans (1939)

observed that excision of the sympathetic chain in dogs with neurogenic hypertension produced only a partial fall of blood pressure providing the splanchnic innervation of the kidneys remained intact. Subsequent denervation of the kidneys produced a fall of blood pressure to normal levels Grimson (1940) confirmed these findings These results appeared to indicate that an increase of sympathetic tone is capable of producing some modification in the kidney which is responsible for the maintenance of the hypertension. It is not clear whether this is attributable to vasoconstriction with resulting renal ischemia or to some other mechanism. The results obtained by Taquini (1938b) do not support the existence of renal ischemia Using the preparation of Läwen-Trendelenburg, he was unable to demonstrate vasoconstrictor substances in the blood of the renal vein in dogs with acute hypertension from section of the pressor regulator nerves. In order to elucidate this point, the presence of renin in the renal venous blood should be investigated.

Thomas (1941) sectioned the pressor regulator nerves in intact and nephrectomized dogs and observed that the rise in pressure which followed immediately after the denervation was not significantly different in the two groups of animals. This apparent contradiction to the results found by other authors may possibly be due to the acute character of Thomas' experiments.

Elaut (1935) observed that renal denervation alone neither prevented nor modified the hypertension produced by section of pressor regulator nerves This confirmed by Grimson (1941). Kin (1939) claimed, however, that renal denervation caused the pressure of rabbits with neurogenic hypertension to return to normal. Hoerner, Fontaine and Mandel (1938) observed no signs of renal insufficiency (blood urea nitrogen, Ambard's constant, phenolsulphonphthalein test) in dogs with neurogenic hypertension of two years' duration. Nowak (1940) observed no abnormalities of the urine of dogs with chronic hypertension of this type. Anatomically, certain renal lesions have been observed in animals with hypertension from section of the pressor receptor nerves (Nordmann, 1929; Goormaghtigh, 1931). Hoerner, Fontaine and Mandel (1938) and Thomas (1944), however, did not observe any renal lesions attributable to this type of hypertension in dogs.

The participation of the renal circulation in the vasomotor reflexes arising in the carotid sinus has been studied by various authors.

According to Unna (1935), Hartmann, Ørskov and Rein (1937) and Schneider and Wildbolz (1937), the renal circulation does not take part in the vasomotor reflexes of the carotid sinus while Handovsky and Samaan (1939) and Malméjac and Donnet (1939) claim that it is possible to observe vasoconstriction

In regard to the relationship between neurogenic and renal hypertension, Grimson (1942) suggested the following hypothesis in order to explain hypertension in man: (1) disturbances of the pressor receptor mechanism by psychic, somatic, or visceral stimuli may initiate a rise of blood pressure without at first producing anatomic changes in the vascular system; (2) the persistent hypertension eventually produces vascular sclerosis, and (3) the kidney becomes altered as a result of changes in the renal arterioles As Grimson pointed out, however, this succession of events is purely hypothetical and further studies are necessary before they can be considered as proven

In summary, therefore, we can say that arterial hypertension produced by section of the pressor receptor nerves is due to an increase in tone of the sympathetic nervous system due to the absence of reflex tonic action This hypertonicity may possibly be due to secretion of adrenalin or sympathin The relation between the kidney and this type of hypertension is not clear and requires further study.

This type of hypertension is somewhat different from that of renal origin The tachycardia and marked cardiac hypertrophy, which have been described in the former, are not characteristic of the latter. The hypertension from renal ischemia is not modified by total sympathectomy as will be seen later The following monographs on neurogenic hypertension can be consulted by those who are interested. Heymans (1938a, b), Heymans and Bouckaert (1939), Delrieu (1939) and Grimson (1941).

HYPERTENSION OF CENTRAL ORIGIN

Dixon and Heller (1932) and Heller (1934) reported prolonged hypertension in dogs following the intracisternal injection of a suspension of kaolin According to these investigators, this type of hypertension of central nervous origin is secondary to the increased intracranial pressure produced by obstruction of the subarachnoid spaces. These results have been confirmed by Hoff (1935) in dogs, and by Giordano and Galigani (1937, 1939), Griffith, Jeffers and Lindauer (1935) and Griffith and Roberts (1938) in rats The latter authors

demonstrated the existence of a lymphatic block and increase in the spinal fluid pressure. According to Braun (1933) and Braun and Samet (1934, 1935a, b), renal denervation is capable of preventing or curing this type of hypertension. Jeffers, Lindauer and Lukens (1937) claimed that bilateral adrenalectomy did not prevent the development of this hypertension if cortical extracts and sodium chloride were administered Pick (1935) and Vogt (1938) reported the existence of vasoconstrictor substances in the blood of these animals Lindauer, Griffith and Jeffers (1938) claimed that the administration of ergotamine tartrate produced a fall of blood pressure in rats with hypertension produced by increased intracranial pressure.

In contradistinction to the results described above, Foà, List and Peet (1941) were not able to produce a lasting elevation of blood pressure in dogs from the injection of kaolin. In only half of the cases did they obtain moderate elevations of blood pressure, and in these it did not persist for more than three weeks. At autopsy, however, the existence of a typical hydrocephalus was demonstrable. These investigators believed that the method of recording blood pressure might have been responsible for these differences. They used direct arterial puncture in trained dogs Lambert and Wakerlin (1942) were also unable to produce persistent hypertension in rats, rabbits and dogs from the intracisternal injection of kaolin, and Lindauer and Griffith (1938) were unable to produce hypertension in the cat by this method.

In considering the hypertension produced by increased intracranial pressure, the acute rise, which is produced immediately after elevating the spinal fluid pressure and which persists for a variable time, must be distinguished from the chronic elevation of the blood pressure The former is an accepted finding and was demonstrated by Cushing (1903) and was confirmed recently by Freeman and Jeffers (1939, 1940). Forster (1943) has shown that in order to obtain a rise in pressure the medullary centers must remain intact. In regard to permanent hypertension, the contradictory results noted above make it necessary to judge the reported results with caution.

CHRONIC HYPERTENSION FROM CEREBRAL ISCHEMIA

According to Nowak and W[illegible]er (1939), chronic hypertension in dogs may be produced by [illegible] the carotid, vertebral and spinal arteries. Fo[illegible]ing this pi[illegible] the collateral circulation is in-

sufficient and produces cerebral ischemia which is then responsible for the hypertension. Fishback, Dutra and MacCamy (1943) have recently confirmed these results

HYPERTENSION PRODUCED BY STEROLS

In the year 1912, Fahr observed arteriosclerotic lesions and arterial hypertension in rabbits following the daily administration of egg yolk. Van Leersum (1912) produced rises of blood pressure as a result of a diet of ground-up liver, and his results were confirmed by Schmidtmann (1922), who attributed it to the amount of cholesterol contained in the diet. Schonheimer (1924) supported this concept by observing rises of blood pressure in some animals on a high cholesterol diet Shapiro and Seecof (1925) were unable to produce elevations of blood pressure by this means but did produce arteriosclerosis Lowenthal (1926) observed that the majority of rabbits fed with diets rich in cholesterol developed lesions of arteriosclerosis, and in some a rise of blood pressure appeared.

Appelrot, in 1933, found that the administration of massive doses of vitamin D_2 to dogs produced a rise of blood pressure Handovsky (1937) confirmed these results, finding that the oral administration of calciferol in a dosage of 100 to 700 gamma per kilo per day produced hypertension in dogs Following the withdrawal of calciferol, blood pressure returned to normal after a variable length of time The anatomic studies of Handovsky and Goormaghtigh (1935) and Goormaghtigh and Handovsky (1938) revealed hypertrophy of the smooth muscle fibers of the media of the arterioles of various organs, such as the kidney, spleen, and the like These lesions were particularly prominent in the kidney where arteriolo-necrosis was observed with or without a concomitant nephritis according to the dose of calciferol employed Signs of hyperfunction of the thyroid were observed with doses up to 250 gamma and those animals which received a dosage of 70 gamma or more showed a hypersensitivity to the pressor action of adrenalin Mrazek, Novak and Reed (1942) and Ham (1940) obtained hypertension in rats by the administration of vitamin D or desoxycorticosterone More recently, Katz, Rodbard and Meyer (1943) and Mrazek, Jensik and Reed (1944) were unable to produce hypertension in dogs by the administration of vitamin D.

Grollman, Harrison and Williams (1940b) found that the administration of estradiol, testosterone, desoxycorticosterone, progesterone

or diethylstilbestrol produced hypertension in some rats. Blackman, Thomas and Howard (1944) observed *no rise of blood pressure* from the administration of testosterone propionate. Selye (1939, 1942) has shown that certain steroid hormones exert a specific renotropic action and that depending upon the chemical structure of the steroids, they may produce tubular hypertrophy and hyperplasia with improvement of kidney function and no sign of hypertension (true renotropic action) or nephrosclerosis with hypertension (nephrosclerotic action) (Selye, 1942, Selye and Stone, 1943; Selye, Hall and Rowley, 1943, Selye and Pentz, 1943; Selye and Hall, 1944) The most active representatives of compounds exhibiting a true renotropic action were some of the androstane derivatives, while, among many steroids examined, desoxycorticosterone acetate proved to be the most potent in producing nephrosclerosis in several species of animal. Extrarenal vessels, especially the medium-sized pancreatic arteries, may be affected (Selye, Hall and Rowley, 1943). The administration of sodium chloride in large amounts sensitized the animals to this action of desoxycorticosterone (Selye, 1943a; Selye and Stone, 1943; Selye and Hall, 1943; Selye, Hall and Rowley, 1943) Selye and Rowley (1944) prevented the nephrosclerotic action of desoxycorticosterone by the simultaneous administration of methyltestosterone indicating that the nephrosclerotic and renotropic actions of steroids are independent of each other and actually antagonistic. Beland, Mason and Selye (1943b) subjected heminephrectomized rats to cold, exercise and injections of formalin and noted the development of adrenal hypertrophy and hypertension. The authors attributed the hypertension to increased corticoid production in association with sensitization from previous unilateral nephrectomy Rodbard and Freed (1942) also obtained rises of blood pressure in dogs with desoxycorticosterone. This has been confirmed by Briskin, Stokes, Reed and Mrazek (1943) in rats. These authors were unable to obtain elevations using other sterol preparations. The daily injection of diethylstilbestrol, a synthetic estrogen, in spite of not being a sterol, produces hypertension in rats according to Leathem and Drill (1943). They observed a fall of pressure with the same substance in hypophysectomized rats Neither Gaudino (1944) nor Braun-Menéndez and Foglia (1944) obtained hypertension in the normal rat by administering desoxycorticosterone. Perera, Knowlton, Lowell and Loeb (1944) observed that 11 of 23 patients with Addi-

son's disease and 3 patients without adrenal disease treated with desoxycorticosterone developed blood pressures in excess of 140 mm. Hg systolic and 90 mm Hg diastolic, which was not correlated with excessive salt and water retention or with a positive cold pressor test.

The experiments discussed above indicate that a series of substances, with the common characteristic of possessing a phenanthrene nucleus or similar structure, are capable of producing hypertension in a number of species when administered in sufficient dosage The mechanism of this hypertension has not been elucidated. The arteriolar lesions encountered and the hypersensitivity to adrenalin perhaps play some rôle. Bearing in mind the anatomic lesions described by Handovsky and Goormaghtigh, renal involvement in the pathogenesis of this hypertension appears probable.

In support of the renal origin of this type of hypertension, Taquini (1938b) observed vasoconstrictor action in the renal venous blood of a dog made hypertensive by the ingestion of calciferol in contrast to negative findings in a dog without hypertension treated in the same manner. Grollman, Harrison and Williams (1940b) reported curing this type of hypertension in rats by means of renal extracts.

HYPERTENSION PRODUCED BY EXPERIMENTAL MODIFICATIONS OF RENAL FUNCTION

Numerous experimental procedures have been devised for the production of hypertension of renal origin The results have varied according to the method used, the technique utilized for the determination of blood pressure, the species of animal employed, and so forth. Generally speaking, it can be stated that none of the procedures described before the work of Goldblatt and his collaborators was capable of producing permanent hypertension with the regularity necessary for undertaking a systematic study. The rises obtained in most instances were slight and transient, and in the majority the blood pressure was measured by methods of dubious accuracy and were subject to considerable individual variation. For this reason we will consider them only briefly, pointing out the importance which they may have in the interpretation of renal hypertension

NEPHROTOXIC SUBSTANCES. Beckmann (1925) was able to produce nephritis and elevation of blood pressure in rabbits through the use of diphtheria toxin and uranium salts. Dominguez (1928),

or diethylstilbestrol produced hypertension in some rats. Blackman, Thomas and Howard (1944) observed no rise of blood pressure from the administration of testosterone propionate. Selye (1939, 1942) has shown that certain steroid hormones exert a specific renotropic action and that depending upon the chemical structure of the steroids, they may produce tubular hypertrophy and hyperplasia with improvement of kidney function and no sign of hypertension (true renotropic action) or *nephrosclerosis with hypertension* (nephrosclerotic action) (Selye, 1942; Selye and Stone, 1943; Selye, Hall and Rowley, 1943; Selye and Pentz, 1943; Selye and Hall, 1944). The most active representatives of compounds exhibiting a true renotropic action were some of the androstane derivatives, while, among many steroids examined, desoxycorticosterone acetate proved to be the most potent in producing nephrosclerosis in several species of animal. Extrarenal vessels, especially the medium-sized pancreatic arteries, may be affected (Selye, Hall and Rowley, 1943). The administration of sodium chloride in large amounts sensitized the animals to this action of desoxycorticosterone (Selye, 1943a; Selye and Stone, 1943; Selye and Hall, 1943, Selye, Hall and Rowley, 1943) Selye and Rowley (1944) prevented the nephrosclerotic action of desoxycorticosterone by the simultaneous administration of methyltestosterone indicating that the nephrosclerotic and renotropic actions *of steroids are independent of each other and actually antagonistic.* Beland, Mason and Selye (1943b) subjected heminephrectomized rats to cold, exercise and injections of formalin and noted the development of adrenal hypertrophy and hypertension. The authors attributed the hypertension to increased corticoid production in association with sensitization from previous unilateral nephrectomy. Rodbard and Freed (1942) also obtained rises of blood pressure in dogs with desoxycorticosterone. This has been confirmed by Briskin, Stokes, Reed and Mrazek (1943) in rats. These authors were unable to obtain elevations using other sterol preparations. The daily injection of diethylstilbestrol, a synthetic estrogen, in spite of not being a sterol, produces hypertension in rats according to Leathem and Drill (1943). They observed a fall of pressure with the same substance in hypophysectomized rats. Neither Gaudino (1944) nor Braun-Menéndez and Foglia (1944) obtained hypertension in the normal rat by administering desoxycorticosterone. Perera, Knowlton, Lowell and Loeb (1944) observed that 11 of 23 patients with Addi-

Corcoran and Page (1941), on the contrary, have not observed rises of pressure in dogs with nephritis produced by nephrotoxic serum.

SURGICAL REDUCTION OF RENAL PARENCHYMA The effect of bilateral nephrectomy on arterial pressure has been the object of numerous investigations The animals die after four or five days without showing elevation of blood pressure (Backman, 1916a, b, in cats, and Cash, 1926; Hartwich, 1930, Goldblatt, 1937a; Dicker, 1937b, and Houssay and Taquini, 1938b, in dogs). In many instances a fall of pressure is actually observed as in our cases and in those of Verney and Vogt (1938) and Harrison, Mason, Resnik and Rainey (1936) According to Winternitz, Mylon, Waters and Katzenstein (1940), if the trauma of operation is kept at a minimum by carrying out nephrectomy in two stages, more prolonged survival can be obtained—seven or more days—without appreciable change in the blood pressure Blalock and Levy (1937) made an extensive study on dogs with extirpation of one kidney and explantation of the other. Removal of the explanted kidney under local anesthesia did not produce alterations of the pressure for the time that the animal survived. These experiments are interesting because they appear to indicate that the kidney is not necessary for the maintenance of normal blood pressure

Katz, Friedman, Rodbard and Weinstein (1939) observed that nephrectomy initiated a transient rise of the blood pressure from five to six hours following operation This they attributed to a reflex mechanism

Jeffers, Lindauer, Twaddle and Wolferth (1940) found that totally nephrectomized rats, parabiotic with normal rats, survived 20 to 90 days after the second nephrectomy, showing a progressive loss of weight and uremia, and in the last week an increase of blood volume and a terminal hypertension

In summary, therefore, it may be concluded from the experiments discussed above that the retention of metabolites produced by complete renal insufficiency is not capable of initiating a rise of blood pressure

Unilateral nephrectomy, as is well known and as we have repeatedly confirmed, is not followed by any appreciable change of blood pressure or of renal excretory function. Neither in unilateral nor in bilateral nephrectomy are the conditions of chronic renal insufficiency

using uranium, produced generalized arteriosclerotic lesions in rabbits but the blood pressure was normal in all of the animals except one in which severe renal sclerosis and hypertension were present. Arnott and Kellar (1935) obtained transitory elevations of blood pressure in rabbits from injections of sodium oxalate. Later (1936) they reported that renal denervation abolished this hypertension. Israel (1938), using potassium oxalate in rabbits, showed that such rises did not occur in all animals. Scarff and McGeorge (1937), on the other hand, were unable to reproduce the results of Arnott and Kellar. Israel (1938) was unable to produce rises of blood pressure in rabbits using such other nephrotoxic substances as mercury, bismuth, and the like. Dicker (1935) was the only investigator to produce elevations of blood pressure by the injection of streptococcus toxin in dogs The rises obtained were slight and transitory. Although Fouts and Page (1942) were unable to obtain hypertension following the administration of lead salts, Griffith and Lindauer (1944) were able to obtain hypertension from lead in all their rats surviving 40 days or more.

Studies have been made on the effect of injecting nephrotoxic substances into the renal artery. Friedman and Katz (1938) produced nephritis by the injection of trypsin into this vessel, observing only a slight elevation of blood pressure during the acute phase The animals which survived showed renal insufficiency without hypertension Dicker (1937a) observed rises of pressure from the injection of sclerosing substances into the renal artery.

Of particular interest are the results obtained with the so-called nephrotoxic serums prepared by the repeated injection of renal extracts of one species of animal into another. Antibodies in the serum of the injected animal are thereby produced. The injection of this anti-kidney serum produces renal lesions which reproduce those found in glomerulonephritis and undergo the same evolution. Masugi (1934) showed that the injection of duck serum, nephrotoxic for the rabbit, not only produced lesions of glomerulonephritis, but also a slight elevation of blood pressure These results have been confirmed and amplified by Arnott, Kellar and Matthew (1936), Hamori and Koranyi (1938) and Kay (1940a, b, 1942) and Kay, Lucchesi and Rutherford (1941) in the rabbit, and by Smadel (1937) and Smadel and Farr (1937) in rats. Kay states that the frequency of hypertension is related to the degree of nephritis. Fouts,

of cases have produced a slight transitory hypertension (Cash, 1924; Mark and Giesendorfer, 1930; Hantschmann, 1931; Ferris and Hynes, 1931).

COMPLETE OCCLUSION OF THE RENAL ARTERY OR OF ITS BRANCHES. Katzenstein (1905) obtained slight rises of blood pressure in rabbits and dogs by complete occlusion of both renal arteries. Similar results were obtained in dogs by Cash (1926), Goldblatt (1937a), Dicker (1937b), Blalock and Levy (1937) and Winternitz, Mylon, Waters and Katzenstein (1940) These results take on greater significance when compared with those obtained by bilateral nephrectomy. In both cases the animals die in uremia at the end of several days, but the arterial pressure falls or is unaltered in nephrectomized animals while it is elevated in those in which the renal arteries are ligated. This may be attributed to the reabsorption through the collateral circulation or lymphatics of pressor substances produced by the kidney undergoing autolysis. The existence of such pressor substances in kidneys after complete ischemia has been demonstrated by Dicker (1937d) and Taquini (1938a) and corroborated by numerous investigators (Collins and Hamilton, 1940a, b; Friedberg, Landowne and Rodbard, 1940, and Prinzmetal, Lewis and Leo, 1940a, b, and others).

Complete occlusion of the renal artery on one side in the dog has produced only transitory elevation of blood pressure.[3] Pickering and Prinzmetal (1938b) obtained negative results in rabbits. As in the case of bilateral ligation of the renal arteries, the hypertension observed in dogs may be due to the reabsorption of pressor substances by way of the collateral circulation Indeed, Verney and Vogt (1938) observed that the elimination of this collateral circulation prevented the rise of pressure produced by ligation of the artery of one kidney.

Ligation of several of the branches of the renal artery has been carried out with the object of producing partial necrosis of the kidney. The results have in general been accompanied by transitory rises of blood pressure[4]

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[3] Friedmann and Wachsmuth, 1930, Hartwich, 1932, Hartwich and Hessel, 1932; Konzett and Unna, 1937, Verney and Vogt, 1938, Robbers and Westenhoeffer, 1939, and Winternitz, Mylon, Waters and Katzenstein, 1940

[4] Janeway, 1908, 1913, Mark, 1928, Hartwich, 1930, Friedmann and Wachsmuth, 1930, Wolf and Heinsen, 1935; Konzett and Unna, 1937, and Verney and Vogt, 1938

eproduced. In order to do this, it is necessary to excise a variable mount of renal tissue according to the species employed. The hyper-ensive action of these subtotal nephrectomies differs according to he species

In the dog, reduction of renal mass has produced only slight and ransitory rises of pressure.[1] Backman (1916a, b) claimed to have btained elevations in cats, while Anderson (1926) observed no rise n rabbits.

In the rat, all investigators agree as to the possibility of producing hronic hypertension through surgical reduction of the renal paren-hyma.[2] Ample excision of up to five-sixths of the kidney of the rat (Chanutin and Ferris, 1932) can produce polyuria, albuminuria, ematuria, anemia, cardiac hypertrophy, and hypertension. The lood pressure becomes gradually elevated, reaching maximal values fter several months. This type of rise suggests the possibility that he hypertensive effect of reduction of renal substance is due to a econdary process (cicatricial contraction) more than to the reduction f the parenchyma itself

Wood and Ethridge (1933) found that hypertension reached a eak some 60 days after performing subtotal nephrectomy in rats. The kidney showed certain histologic changes, especially in the

eduction of the lumen of the arterioles occurred. Such changes sug-est that in these cases the renal tissue undergoes a certain degree of schemia. Dock and Rytand (1937), however, did not observe a iminution of renal blood flow per gram of kidney in rats with sub-otal nephrectomy.

Other investigators have employed slightly different techniques y combining unilateral nephrectomy and partial excision of the ther with ligation of some of the branches of the renal artery. These procedures have been carried out on dogs and in the majority

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[1] Allen, Scharf and Lundin, 1925; Mark, 1925, 1928, Passler and Heineke, 937. Other authors who were unable to obtain rises are. Brasotti, 1927; Fried-ann and Wachsmuth, 1930, Hartwich, 1932, Allen, Bollman and Mann, 1935, erney and Vogt, 1938; and Mason, Robinson and Blalock, 1940.

[2] Chanutin and Ferris, 1932, Chanutin and Barksdale, 1933, Wood and thridge, 1933, Rytand and Dock, 1935; Harrison, Grollman and Williams, 940, Díaz and Levy, 1939, Griffith and Ingle, 1940, Jensen, Corwin, Tolksdorf, asey, Bamman, 1941, Gómez Salazar, 1942

hypertrophy in rats subjected to irradiation of the kidneys They considered that this was sufficient evidence to indicate the absence of hypertension.

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ARTERIOVENOUS ANASTOMOSIS OF RENAL VESSELS. Major, Weber and Rumold (1939) obtained hypertension and renal insufficiency in three dogs by anastomosing the vessels of one kidney and removing the other kidney The animals survived only a few days.

OCCLUSION OF THE URETERS. Rautenberg (1910) observed albuminuria and prolonged hypertension in rabbits by ligating one ureter for three weeks Pickering and Prinzmetal (1938b) were unable to obtain a rise of blood pressure in the rabbit by ligating one ureter only The kidney showed diffuse fibrosis Hartwich (1930) produced hypertension which appeared within three hours of the ligation of both ureters in dogs Unilateral ligation was effective in some cases Dicker (1937e) confirmed the rise of pressure from bilateral ureteral ligation and found that it was not prevented by renal denervation Rises of blood pressure in dogs by ligation of the ureters have also been observed by Harrison, Mason, Resnik

These results appear to indicate sufficiently clearly the possibility of obtaining transitory elevations of blood pressure by a more or less extensive blocking of vascular areas of the kidney In the light of the experiments of Goldblatt, its mechanism of production appears understandable. Those areas in which the circulation has been disturbed develop a condition of incomplete ischemia due to the collateral circulation which they receive. When reabsorption of the necrosed areas has become complete, or when the collateral circulation becomes adequate, ischemia and hypertension disappear

MULTIPLE RENAL EMBOLI Injections of suspensions or emulsions into the renal artery give rise to the formation of areas of infarction of variable size In some, all of the kidney is involved in the necrotic process and death of the animal ensues; in others, the lesions are more localized and the animals survive a longer time Attempts have been made to produce hypertension with multiple emboli by using emulsions of bismuth, oil or paraffin (Senator, 1911).

Cash (1924) using Berlin blue, and Apfelbach and Jensen (1931) using carbon, were unable to produce hypertension in dogs. Maegraith and McLean (1938) reported prolonged elevations of blood pressure in rabbits following the injection of a suspension of kieselguhr into the renal artery on one side only Cressmann and Blalock (1939) were unable to produce rises of pressure in dogs even though they injected kieselguhr into both renal arteries.

IRRADIATION OF THE KIDNEY BY X-RAYS Hartman, Bolliger and Doub (1929) demonstrated that x-rays produce renal lesions and moderate rises of blood pressure in dogs Histologically there was destruction of renal parenchyma, fibrosis, and diffuse endarteritis These lesions had already been observed by O'Hare and collaborators in 1926. Page (1936b) irradiated kidneys which had been explanted under the skin These dogs developed loss of weight, debility, albuminuria, cylindruria and hematuria. Definite elevation of blood pressure occurred except during the terminal stage. The kidneys showed atrophy of the cortex, fibrosis, and necrosis of the loops of Henle Avascular glomeruli were observed as well as perivascular fibrosis.

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and Rainey (1936), Blalock and Levy (1937), Megibow, Friedberg, Rodbard and Katz (1940), Megibow and Katz (1941) and Megibow, Katz and Rodbard (1942). Levy, Mason, Harrison and Blalock (1937) studied the effect of ureteral occlusion on the circulation and on the consumption of oxygen by the kidney in unanesthetized dogs. They found that bilateral occlusion produced a rise of blood pressure in only three of eight dogs studied. In all of the animals, a

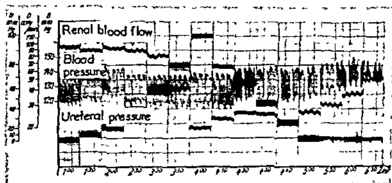


FIGURE 5 LIGATION OF URETER AND RENAL BLOOD FLOW

Blood flow from the renal vein was measured with a thermostromuhr after ligation of the ureter. U, ureteral pressure, D, renal blood flow; B, blood pressure Time in hours Note that by increasing ureteral pressure renal blood flow is reduced, and by decreasing ureteral pressure there is an increase of renal blood flow (After Enger, Gerstner and Sarre, Zentralbl f inn Med, 1937, *58*, 865).

decrease of approximately 41 per cent in renal blood flow was observed

These results were in accord with the observations of Enger and Gerstner (1938) and Enger, Linder and Sarre (1938a, b) who obtained a rise of blood pressure in dogs by grafting kidneys, *the ureters* of which had been ligated A diminution of renal blood flow was likewise observed in these animals (see figure 5). In the rat, Williams, *Wegria and Harrison (1938) observed that spontaneous hydronephrosis* was accompanied by hypertension Schroeder (1942) mentioned that he had obtained hypertension in rats by producing *hydronephrosis* by partial constriction of the ureters.

Eichelberger (1938, 1939) produced no hypertension in dogs with unilateral nephrectomy and contralateral hydronephrosis produced

by partial constriction of the ureter of one kidney, even though the animals were followed for several weeks after the operation According to Megibow, Katz and Rodbard (1942) partial bilateral ureteral compression produced only transitory elevations of blood pressure in dogs.

Goldblatt and Kahn (1940, 1941a) studied extensively the effect of ligation of the ureters in dogs. Unilateral occlusion did not produce any elevation of blood pressure Hypertension was not observed in dogs with unilateral renal ischemia and ligation of the ureter of the same kidney In dogs made hypertensive by compression of one renal artery, ligation of the ureter of the same kidney caused the blood pressure to return to normal after several days. Constriction of the artery of one kidney and occlusion of the ureter of the same kidney followed by removal of the opposite kidney produced moderate elevations of pressure which lasted until the death of the animal from uremia These results have been explained by Goldblatt and Kahn by the supposition that the effect of ureteral occlusion on a kidney with the main renal artery constricted interferes with the rate of passage of pressor producing substances from the kidney into the systemic circulation or diminishes the amount produced.

The possibility that hydronephrosis can produce permanent vascular changes in the kidney was studied histologically by Hinman and Morison (1926) Winternitz and Katzenstein (1940) observed intra- and peri-renal vascular lesions, venous thrombosis, infarction of the kidney, hyalin necrosis of the glomerular capillaries, and necrotizing arteriolitis in other organs following ligation of the ureters in dogs.

It appears, therefore, that occlusion of the ureters produces a state of renal ischemia which is responsible for the formation of pressor substances These are liberated into the circulation with difficulty because of the conditions created by the hydronephrosis Hypertension would therefore appear only under certain circumstances such as when the occlusion is carried out on both kidneys or unilaterally in association with removal of the other. (This will be more easily appreciated after consulting the section describing the protective action of the normal kidney.)

INTERMITTENT OCCLUSION OF THE RENAL PEDICLE. Loesch (1933) studied the effect on blood pressure of intermittent

compression of the renal pedicle in dogs with kidneys previous explanted subcutaneously The compression was performed eve two or three days for a maximal period of 30 minutes. After a certa length of time, albuminuria, nitrogen retention and hypertensic occurred which persisted even after the compressions were stoppe Since it appeared strange that intermittent occlusion of the circul tion was capable of producing persistent hypertension, Goldbla Weinstein and Kahn (1941) repeated these experiments using different technique Hypertension and renal insufficiency were o served only when the artery was permanently constricted either acc dentally or intentionally For this reason they attributed the resul of Loesch to a possible permanent constriction of the artery as result of the explantation or of lesions produced by the compressio Allen (1943), on the other hand, insisted that chronic hypertensio could be obtained by intermittent occlusion of the renal pedicl

PARTIAL OCCLUSION OF THE AORTA (COARCTATIO OF THE AORTA) Goldblatt and Kahn (1938) and Goldblat Kahn and Hanzal (1939) demonstrated that constriction of the ab dominal aorta immediately above the origin of the renal vessels n dogs produced a permanent rise of the carotid arterial pressur without modification of the femoral pressure. Immediately after th aortic constriction hypotension developed distal to the aortic com pression without modification of the carotid pressure At the end o several hours, a rise of pressure both above and below the constrictior occurred Finally a frank hypertension developed above the constric tion and a normal pressure or only slightly elevated pressure was found below the point of constriction If the aortic compression was carried out below the origin of the renal arteries, hypertension did not ensue As a result of these findings, the authors believed that this type of hypertension was due to renal ischemia which was produced by the aortic compression

The relationship between experimental and human coarctation of the aorta will be discussed in a later section. At this point it is of interest to consider if this type of experimental hypertension can be attributed to renal ischemia The work of Goldblatt has been confirmed by Rytand (1938a, b) in rats This investigator used cardiac hypertrophy as a criterion of hypertension because of the findings

of Chanutin and Ferris (1932) who observed a correlation between the weight of the heart and the blood pressure in rats with hypertension from subtotal nephrectomy Rytand concluded that in order to produce hypertension (cardiac hypertrophy), coarctation of the abdominal aorta had to produce renal ischemia Brotchner (1939a, b) in acute experiments observed that aortic compression produced an immediate rise of blood pressure which was independent of the presence of the kidneys and was due exclusively to essentially mechanical factors Barcroft (1931) and Barcroft and Formijne (1934) demonstrated increases of blood pressure which were entirely mechanical in origin by compression of the thoracic aorta in acute experiments Steele (1939) observed that constriction of the aorta above the origin of the renal arteries was followed by a persistent elevation of the diastolic pressure not only in the carotid arteries but in the femorals as well

He concluded that the hypertension was on the basis of a generalized arterial constriction as occurs following renal ischemia Ogden, Page and Hildebrand (1942) concluded from their experiments carried out on cats and dogs that complete occlusion of the aorta above the renal arteries produced two types of pressure rise. (a) an immediate increase from mechanical factors which occurred inconstantly, and (b) a slower increase due to renal ischemia

Page (1940b) confirmed the results of Goldblatt on compression of the abdominal aorta in dogs He was unable to produce hypertension above the point of constriction, however, if the aortic compression was carried out at the level of the arch of the aorta This was attributed by this investigator to the abundant collateral circulation which is rapidly formed under these conditions and which assures a sufficient renal circulation

We believe that the studies mentioned above allow us to conclude that chronic hypertension produced experimentally by constriction of the abdominal aorta immediately above the origin of the renal arteries is attributable to a concomitant renal ischemia

RENAL COMPRESSION AND PERINEPHRITIS Alwens (1909) *demonstrated that compression of the cat kidney by an oncometer* produced a slight rise of blood pressure in acute experiments

Page (1939b, c) produced persistent hypertension in dogs, cats and rabbits by enveloping the kidneys in cellophane or silk Three

five days after performing the operation, the tissues react to these foreign bodies forming within two or three weeks an actual fibro-collaginous shell which compresses the renal parenchyma. Three to five weeks are usually necessary to obtain pronounced rises of pressure. These results have been confirmed by Hermann, Jourdan and Vial (1940) Greenwood, Nassim and Taylor (1939) obtained hypertension in dogs by enclosing the kidney in collodion.

In rats, Friedman, Jarman and Klemperer (1941) and Schroeder

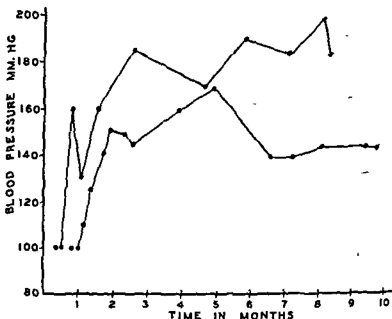


FIGURE 6 HYPERTENSION FROM PERINEPHRITIS

Blood pressure of two rats after wrapping the left kidneys with gauze soaked in collodion Note that the hypertension is persistent although the opposite normal kidney is intact (Gaudino, Rev Soc. argent de biol 1944, *20*, 460).

(1942) obtained hypertension by means of cellophane perinephritis Herrmann, Decherd and Erhard (1941) observed that perinephritis produced by collodion in rats was followed by the development of cardiac hypertrophy which was taken as an index of hypertension They did not observe rises in rats, however, with perinephritis from cellophane. Dell'Oro (1942a, b) and Gaudino (1944) did obtain hypertension in rats by means of collodion (figure 6). Kempf

and Page (1942) and Grollman and Williams (1942) likewise obtained excellent results by enveloping the kidneys with silk. Gómez-Salazar (1942), studying different materials in rats, found that cellophane and rayon produced hypertension with greater frequency than did collodion.

Grollman and Rule (1943) produced hypertension by perinephritis in one of a pair of parabiotic rats In some cases, the hypertension was transmitted to the normal animal, although the level of pressure reached was less than in that of the rat with the perinephritis Schroeder (1942) explanted the left kidney of rats into a fold of skin in the flank and produced hypertension in most of the animals by traumatizing the kidney with light strokes of a hammer. Grollman (1944b) produced hypertension in rats, rabbits and dogs by passing a cotton thread or tape over the pole and body of the kidney and drawing it taut.

The importance of these studies in rats is evident when one considers the difficulties involved in producing renal ischemia in an animal of such small size

The mechanism of experimental hypertension produced by perinephritis appears to depend upon the constrictive action of the fibroblastic envelope formed Under these circumstances, renal ischemia would be produced, albeit by a mechanism quite different from that of partial compression of the renal artery Similarity in the behavior of this type of hypertension and that produced by a Goldblatt clamp supports this view (Page, 1939b, c) Graef and Page (1940) did not observe lesions of ischemic origin in the first stages of experimental perinephritis In the advanced stages, however, ischemic cicatrices appeared which were attributed to disturbances of the capillary circulation either from compression of the kidney or from compression of the hilar vessels by the cicatricial tissue Determinations of renal blood flow should be conclusive in settling this question.

A series of procedures has just been mentioned which, through its action on the kidney, is capable of producing an elevation of blood pressure We have already referred in another section to the difficulty of producing permanent hypertension in animals before the work of Goldblatt, Lynch, Hanzal and Summerville (1934). At the present time, the results obtained by procedures which produce renal lesions can be interpreted as due to the production of

renal ischemia. In each paragraph we have mentioned the arguments on which such a supposition is based. Generally speaking, the period of time which is necessary to produce a pressor effect in a given procedure coincides with that which one would anticipate if the pressor action were attributable to ischemia. In subtotal nephrectomy in the rat or in perinephritis, for example, the hypertension appears gradually after the operation The reduction of renal mass in rats according to Grollman and Williams (1942) is apt to be much more effective in producing hypertension when the amount of cicatricial tissue produced is great The fact that many of the rises of pressure following the procedures described are transitory can be explained by the formation of a collateral circulation. Although Corcoran and Page (1941a, b) believe that partial constriction of the renal artery can produce hypertension without ischemia, it would appear logical to us to attribute an identical mechanism to all the hypertensions of renal origin Naturally in order to demonstrate the existence of ischemia in each one of the experimental conditions studied, it is necessary to measure the renal blood flow which has not as yet been done

These considerations justify the use of Goldblatt's method for the generic study of renal hypertension.

INCOMPLETE RENAL ISCHEMIA. The idea of producing ischemia of renal tissue by means of constricting the lumen of the renal artery dates from the year 1905 when Katzenstein noted a slight elevation of blood pressure in dogs as a result of partial constriction of the renal artery. Bridgman and Hirose (1918), on the other hand, did not observe a rise of blood pressure from constriction of one renal artery and contralateral nephrectomy. Both investigations were carried out in acute experiments, although Bridgman and Hirose mentioned the interest which would ensue upon prolonged experiments which would simulate a chronic lesion. To Goldblatt, Lynch, Hanzal and Summerville (1934) is due the credit of demonstrating conclusively that localized ischemia of renal tissue is capable of producing persistent hypertension in the dog They not only contributed a proof of the important rôle of the kidney in hypertension, but also devised an experimental method for the study of this disease. The work of Goldblatt and collaborators, published in the year 1934,

was rapidly confirmed and amplified by numerous investigators.[5] By the use of this method, hypertension has been produced in the following animals. in the monkey by Goldblatt (1937b); in rabbits by Pickering and Prinzmetal (1938b), Drury (1938), Rytand (1938a, b), Wilson and Pickering (1938) and McLean and Maegraith (1939); in goats and sheep by Taquini (unpublished) and more recently by Goldblatt, Kahn and Lewis (1943), in rats by Rose and Weil (1939), Schroeder (1942) and Kempf and Page (1942) Apart from these early confirmations of the results obtained by Goldblatt in the dog and in other species, numerous other publications have appeared which will be cited presently Vogt (1940) was not able to obtain permanent renal hypertension in the frog On the basis of the present interpretation of the mechanism of production of renal hypertension, this negative result is explainable by the lack of renin in the kidney of this animal (see Chapter IV)

Methods.—The method employed by Goldblatt, Lynch, Hanzal and Summerville (1934) for producing renal ischemia consisted of applying a small adjustable silver clamp as shown in figure 7. A screw allowed the degree of constriction to be regulated to the desired degree of ischemia. The quantitative evaluation of the degree of ischemia during the operation offers certain difficulties owing to the difference in size of the renal arterial trunks or of the collaterals in different animals One may speak, however, of pronounced ischemia, medium ischemia, or slight ischemia depending upon the degree of constriction employed.

The operation is carried out under general anesthesia, preferably by the extraperitoneal lumbar route, retracting the kidney without separating it from its attachments and freeing the renal artery in order to apply the clamp as closely as possible to the origin of the renal artery at the aorta. One very important precaution is to determine the number of renal arteries present In the dog, it is extremely common for a short trunk to divide into several branches or for two

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[5] Page, 1935a, Collins, 1936, Flaut, 1936a, b, Wood and Cash, 1936 Prinzmetal and Friedman, 1936, Govaerts and Dicker, 1936, Martinetti, 1936, Harrison, Blalock and Mason, 1936, Heymans, Bouckaert, Elaut, Bayless and Samaan, 1937, Houssay and Fasciolo, 1937a b, Child and Glenn, 1937, 1938, Introzzi, Amici di San Leo and Rostto, 1938, Israel, 1938, Verney and Vogt, 1938, and so forth

or even three renal arteries to arise independently from the aorta. Estimation of the degree of ischemia is always difficult and can be determined by inspection of the constriction, or better by palpation of the pulse on both sides of the clamp.

The material from which the clamp is made is also of importance

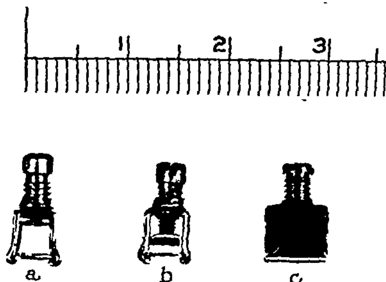


FIGURE 7 CLAMPS FOR CONSTRICTION OF RENAL ARTERIES

Clamp with movable and removable plates and double-acting screw Ordinary type. (a) Movable plate in open position; (b) movable plate partly screwed down, (c) side view. Scale in centimeters (After Goldblatt, Am. J. Clin Path., 1940, *10*, 40).

since some metals produce necrosis of tissue. Goldblatt advocates the use of pure silver.

Naturally, many modifications of the technique are possible without altering the principle or the result Collins (1936), for example, produced the constriction by including a wire or a needle of variable thickness in the ligature around the artery. On tying the knot, the wire was withdrawn thereby re-establishing the passage of blood. The degree of ischemia depends naturally on the size of the wire used. Details of the techniques for producing renal ischemia can be found in the writings of Goldblatt and collaborators (1934), Glenn and Child (1938), Introzzi, Amici di San Leo and Rosito (1938), Fasciolo (1939), and Goldblatt (1940).

Unilateral Renal Ischemia.—Constriction of the artery of one kidney produces a rise of pressure which in general begins 24 to 48 hours after the ischemia. The rise continues in the ensuing days to reach its maximum some two to ten days later. Such early rises are not always observed In some animals it is necessary to wait several days before obtaining significant increases When the ischemia is produced in one kidney only in dogs, the hypertension persists in general for several weeks or months, and then gradually returns to normal. In rats, however, persistent rises have been obtained by unilateral ischemia. The reason for the gradual disappearance of the hypertension in animals other than the rat has not been completely elucidated. The formation of a collateral circulation and the protective action of the normal kidney (see Chapter IX) undoubtedly play an important rôle. In those animals in which the opposite kidney remains intact, the elevation of pressure is less than in those in which both arteries are constricted or in those in which one artery is constricted and the opposite kidney removed. Fasciolo (1938a) observed a rise of 47 mm Hg (average of 18 animals) in uninephrectomized dogs with the remaining kidney ischemic, and of 37 mm. Hg (average of 23 animals) when the opposite kidney remained intact. Although these figures were taken from actual experiments under similar conditions and although they were statistically significant, they must be accepted with certain reservation since the degree of ischemia is of basic importance and is difficult to estimate with exactitude There appears to exist an optimum of ischemia above and below which the rises of blood pressure are not maximal.

Onset of Hypertension.—As we have mentioned, the greatest elevation of blood pressure does not immediately follow the application of the clamp. In most cases, it appears one or two weeks later. The degree of renal ischemia must be greatest at the moment of the constriction since it subsequently tends to become reduced because of the formation of a collateral circulation and atrophy of the kidney. There is thus a discrepancy between the time of greatest renal ischemia and of greatest hypertension It is possible that the effects of anesthesia and the trauma of operation counteract the effects of renal ischemia on the blood pressure In order to avoid these criticisms, Grimson (1939) made use of a special type of clamp which was placed on the renal artery and later tightened without

the use of anesthesia or of an operative procedure. By this method, he was able to show that constriction of one or two renal arteries produced a significant increase in the blood pressure in the first two or three hours which followed the constriction. In this way, he confirmed the results obtained by Verney and Vogt (1938) who employed a somewhat similar technique.

In acute experiments under general anesthesia, it has been shown that partial constriction of the renal artery produces a rise of pressure

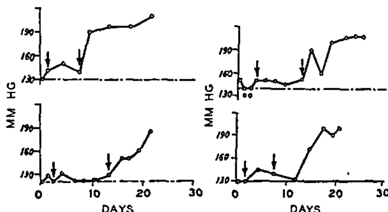


FIGURE 8 HYPERTENSION FROM UNILATERAL RENAL ISCHEMIA

Four observations on removal of one kidney and constriction of the artery of the remaining kidney in dogs The first arrow represents the time of nephrectomy, and the second, constriction of the artery of the remaining kidney The *base lines represent the initial blood pressures Note the rise of blood pressure* when the normal kidney is removed (Modified from Fasciolo, 1939)

within a few minutes (Enger, Linder and Sarre, 1938a, b; Grimson, 1939; Braun-Menéndez and Fasciolo, 1939a) When the ischemia is abolished, the pressure returns to normal within half an hour. Whatever techniques are used in experiments with or without anesthesia, however, pronounced rises of pressure cannot be obtained before 24 hours or more.

Renal Ischemia in Animals with Unilateral Nephrectomy.—If ischemia of one kidney is carried out in dogs, a greater rise of pressure takes place in a shorter period of time if the opposite kidney is removed (Fasciolo, 1938a) (see figure 8) The elevated blood pressure tends to persist in these cases and may remain permanently elevated for years, and Goldblatt (personal communication, 1945) has had dogs with experimental renal hypertension survive for at

least 7 years. In some cases, however, the pressure may fall or become normal after a certain length of time. In these cases, further constriction of the renal artery can restore the hypertension (Goldblatt, Lynch, Hanzal and Summerville, 1934; Dicker, 1937a; Fasciolo, 1939).

The fall of pressure observed after a certain period of renal *ischemia is due to the development of a collateral circulation.* Excision of the collaterals is accompanied by a new rise of blood pressure (Cerqua and Samaan, 1938, 1939, Verney and Vogt, 1938). We have been able to confirm these observations (unpublished results).

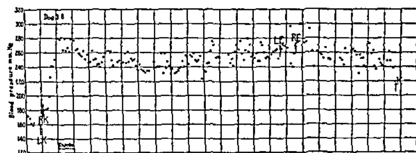


FIGURE 9 HYPERTENSION FROM BILATERAL RENAL ISCHEMIA

Chart showing the blood pressure after severe constriction of the left main renal artery (LK) and severe constriction of the right main renal artery (RK). The left eye was enucleated (LE) thirty-four months after the development of hypertension, and the right eye (RE) was enucleated thirty-six months after the development of hypertension. The blood pressure remained elevated for 50 months following the constriction of both renal arteries The dog was killed (K) because suppurative metritis with pyometrium developed (After Keyes and Goldblatt, Arch Ophth, 1937, *17,* 1010).

Bilateral Renal Ischemia—Constriction of both renal arteries likewise produces permanent hypertension (figure 9) If the constriction is carried out in two stages, the elevation obtained by the first ischemia rises further when the second kidney is made ischemic. Aside from this, the behavior of the animal is similar to that following unilateral renal ischemia. Removal of one of the ischemic kidneys is followed by a further rise of blood pressure, according to Goldblatt, Lynch, Hanzal and Summerville (1934) and Verney and Vogt (1938).

Constriction of both renal arteries does not produce permanent

hypertension in all cases. In some animals, it is necessary to increase the constriction after a time, whereat a definite hypertension almost always follows In some, the collateral circulation may be so well developed that it is necessary to carry out complete occlusion of both renal arteries (Goldblatt, 1937a, Blalock and Levy, 1937) If complete occlusion of the renal arteries is carried out progressively, it is possible to obtain longer survival periods. Under these circumstances, Goldblatt has been able to keep a dog alive for four years with extreme elevation of the blood pressure and only minimal signs of renal insufficiency. In order to obtain a permanent hypertension, the formation of a collateral circulation can be prevented after constricting the renal artery Goldblatt (1940) suggested the use of membrane of lamb cecum as described by Bell and Pedersen (1930). This does not form fibroblastic reactions around the kidney as does cellophane.

In dogs with two renal arteries supplying one kidney, it is possible to constrict only one of them Fasciolo (1939) carried out this procedure in three dogs in which the opposite kidney had been removed or made ischemic previously. The constriction was followed in these three animals by a definite rise of pressure which lasted only a few days. The rapid fall may be explained by the ease with which a collateral circulation within the kidney became re-established.

Removal of the Ischemia —If hypertension from renal ischemia has become established, it disappears if the constriction of the renal artery is removed (Goldblatt, 1937a, Dicker, 1937c, Blalock and Levy, 1937) The pressure usually becomes normal within a few hours In some animals the fall of pressure takes several days to return to normal This has been attributed to the existence of lesions in the renal artery which are capable of maintaining the ischemia (Goldblatt)

Removal of ischemic renal tissue in the dog is followed by a rapid fall of blood pressure to normal levels (Goldblatt, Lynch, Hanzal and Summerville, 1934, Houssay and Fasciolo, 1937b; Blalock and Levy, 1937, Rodbard and Katz, 1939, Verney and Vogt, 1938, 1943) as can be seen in figures 10 and 11 In the rat, on the other hand, removal of the ischemia or of the ischemic kidney producing hypertension may not be followed by a fall of pressure to normal levels (Wilson and Byrom, 1941, Grollman, Harrison and Williams, 1943; Gaudino, unpublished). Patton, Page and Ogden (1943) produced

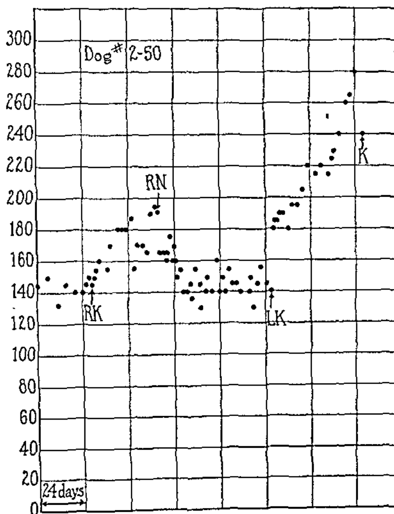


FIGURE 10 REMOVAL OF AN ISCHEMIC KIDNEY AND PRODUCTION OF ISCHEMIA IN THE REMAINING KIDNEY

Mean blood pressure in mm Hg (RK), right main renal artery moderately constricted, (RN), right nephrectomy at a time when the mean blood pressure was elevated resulted in its prompt return to normal (LK), severe constriction of main renal artery of left kidney This was followed by very high *elevation of* mean blood pressure + the mean blood pressure at this time was more than 300 mm Hg (K) killed (After Goldblatt, Ann Int Med, 1937, *11*, 69)

hypertension in rats by means of unilateral renal ischemia. Removal of the ischemic kidney produced no drop in pressure in half of the cases. Only in 20 to 30 per cent did the pressure become normal. In the animals with hypertension of short duration, removal of the ischemic kidney produced a fall in a greater percentage of cases.

Blalock and Levy (1937) studied the time elapsing before the

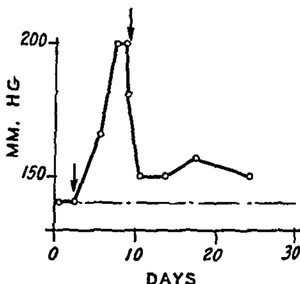


FIGURE 11 EFFECT OF REMOVAL OF THE ISCHEMIC KIDNEY IN A DOG

At the first arrow, the left main renal artery was constricted, and at the second arrow, the left kidney was removed The interrupted line represents the level of the initial blood pressure. Note the rapid fall of blood pressure when the ischemic kidney is removed (Modified from Fasciolo, 1939).

pressure fell to normal when the ischemic kidney was removed. In order to avoid the effects of operation and anesthesia, they first explanted the kidney subcutaneously which allowed them to remove it subsequently through a small incision under local anesthesia. They observed that the arterial pressure generally began to fall within an hour or two of nephrectomy, reaching the initial values in the majority of cases within six to twelve hours Rodbard and Katz (1939), in experiments made under general anesthesia, obtained a fall of blood pressure to normal within six hours of the removal of the ischemic kidney when the opposite kidney remained intact. In those

animals in which the opposite kidney was absent, it took some thirty hours for the pressure to fall to normal.

Having shown that partial ischemia of the kidney is capable of elevating the pressure, it was of importance to ascertain if ischemia of other vascular regions produces changes of blood pressure. Longcope and McClintock (1910) constricted the celiac axis and the superior mesenteric artery without modifying the blood pressure of dogs Later, constriction of other arteries such as the femorals, splanchnics, celiac axis, and so forth was carried out without altering blood pressure (Goldblatt, Lynch, Hanzal and Summerville, 1934; Fasciolo, 1939; Blalock and Levy, 1939). Although constriction of the celiac artery and of both mesenterics was not capable of producing changes in blood pressure, Blalock, Levy and Cressman (1939) observed that if these were combined with renal ischemia, the resulting hypertension appeared to be potentiated and the rises persisted even though the ischemia was unilateral They believed that this effect was due to the difficulty of forming a collateral circulation under such circumstances.

A number of modifications of the renal circulation have failed to prevent the development of hypertension following renal ischemia. Child and Glenn (1938), Levy and Blalock (1938) and Verney and Vogt (1943) anastomosed the renal vein to the portal vein thereby shunting the renal venous blood through the liver before entering into the general circulation This did not prevent the development of hypertension when renal ischemia was induced Other procedures have also been tried without interfering with the pressor effect (Blalock and Levy, 1937)

It is possible to produce permanent hypertension with regularity by resection of the depressor nerves (neurogenic hypertension) or by modifying the renal circulation (renal hypertension) Section of the moderator nerves when performed correctly produces a hypertension which lasts five years or more This type of hypertension is characterized by a marked tachycardia Total sympathectomy almost completely prevents or abolishes this type of hypertension

Partial constriction of the renal artery is capable of producing hypertension which persists for a prolonged period of time. Some investigators have followed cases for at least seven years. This type of

hypertension has been obtained in different species of animals such as dogs, rabbits, rats, goats, sheep and monkeys In the dog, removal of the ischemic kidney or removal of the ischemia is followed by a rapid fall of blood pressure to normal.

The production of perinephritis by cellophane or other material is a satisfactory method of producing hypertension. It is particularly useful in small animals such as the rat in which partial constriction of the renal artery is difficult to perform.

Other procedures which modify renal circulation have been shown to produce small and transitory rises of blood pressure. Subtotal nephrectomy in the rat produces persistent hypertension.

The characteristics of the different types of renal hypertension studied lead to the conclusion that the mechanism of production is probably the same in all.

The administration of large doses of certain substances of biologic importance, in general the sterols, has produced elevation of blood pressure in certain cases

Experimental elevation of intracranial pressure produces hypertension, but the possibility of obtaining a persistent hypertension by this method is subject to doubt Chronic ischemia of the brain, however, has been shown to produce prolonged rises of blood pressure.

CHAPTER II

THE ANIMAL WITH HYPERTENSION FROM RENAL ISCHEMIA

We have seen how permanent hypertension can be produced in different animals by constriction of the renal arteries or by other procedures which alter renal dynamics. A description of the functional and morphologic changes in animals with renal hypertension will be discussed in this chapter This will permit an interpretation later of the mechanism of this type of hypertension. In the great majority of cases, studies have been carried out on dogs made hypertensive by constriction of the renal artery, and on only a few by such procedures as perinephritis, reduction of renal parenchyma, and so forth We believe that all experimental hypertensions of renal origin should be included in the same group although we recognize that it has not been proved that their mechanisms are identical

FUNCTIONAL STUDIES

THE KIDNEY 1) *Methods*—Before referring to changes in renal function in hypertensive animals, we will describe the physiology of renal excretion which is based on the recent development of methods which have been used in intact animals and patients For detailed accounts, we refer the reader to the excellent monographs of Smith (1937, 1940, 1941, 1943a, b), Newton (1939), Winton (1937), Herrin (1941), Bradley (1944), and Goldring and Chasis (1944).

Renal function is accomplished by glomerular filtration and by reabsorption and excretion by the tubules The process of glomerular filtration is a reversible process comparable to the passage of liquid from the capillaries into the interstitial spaces It depends upon the relation between the hydrostatic pressure of the glomerular capillaries on the one hand and the oncotic pressure of the blood colloids and the capsular pressure on the other Variations of glomerular *pressure govern the amount of liquid filtered which is therefore in*dependent within certain limits of the amount of blood passing per

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unit of time. When the pressure in the glomerular capillary is increased as occurs when the efferent vessel *contracts, the amount of* liquid filtered increases despite the fact that there is a diminution in the amount of blood which circulates.

The term glomerular filtrate refers to the total amount of fluid passing across *the glomerular membrane. Since the* water filtered into the glomerulus is reabsorbed in large part by the tubules, the urine volume *represents only a small fraction* of the glomerular filtrate.

Although glomerular filtration is a passive process, tubular reabsorption and excretion are mainly active processes. The excretion of *a substance depends* not only on the amount passing through the kidney, which varies with its concentration in the blood, but also, at a given concentration, on the amount of blood passing through the kidney per unit of time.

Inulin is used to measure the glomerular filtrate. Inulin is a polysaccharide with a molecular weight of about 5,000. This substance is excreted exclusively by glomerular filtration and is not reabsorbed by the tubules. The concentration of inulin in grams per cent is the same in the glomerular filtrate as in the blood plasma. Since it is not reabsorbed by the tubules, the entire amount which is filtered appears in the urine. The total amount of inulin filtered, therefore, depends upon glomerular filtration while its concentration in the urine (gm per cent) depends upon the reabsorption of water by the tubules. Providing the concentration of inulin in the plasma is known, the amount of *inulin* eliminated in the urine *during* a given period is a measure of the amount of fluid filtered by the glomeruli during the same time. *In* other words, the *plasma clearance* of inulin,[1] C_I, i.e., the volume of plasma equivalent to the amount of inulin appearing in the urine in one *minute, is equal to the glo*merular filtrate formed in one minute. The plasma clearance of any substance is expressed by the formula $\frac{U}{P} \times V$ where U equals the concentration of the substance in *the urine;* P, *its concentration in* the plasma, and V, the volume of urine.

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[1] Plasma clearance of [illegible]n C_I; Plasma [illegible] diodrast C_D, Tubular excretory mass TM[illegible]

Diodrast is excreted mainly by the tubules since it passes from the peritubular capillaries into the lumen of the convoluted tubule. When the concentration of diodrast in plasma is low, its excretion is almost complete (85 to 90 per cent). The remaining 10 to 15 per cent which is found in the renal venous blood, represents the volume of plasma flow circulating through non-excretory tissues. Diodrast clearance (C_D) refers to the amount of plasma corresponding to the diodrast eliminated or cleared by the renal parenchyma, and is equal to the amount of plasma passing through the kidney per unit of time, or at least through the functioning tubular areas (effective renal plasma flow).

Phenol red is excreted like diodrast, but less efficiently, since only 50 per cent is extracted from the blood. The plasma clearance of phenol red, therefore, is only about 50 per cent of that of diodrast. Sodium para amino hippurate is likewise excreted like diodrast. At low concentration, Bradley and Curry (1944) and Warren, Merrill and Brannon (1944) found that the extraction ratio varied between 83 and 100 per cent, the average being 84.9 and 88 per cent respectively in normal unanesthetized subjects. The extraction ratio was determined from samples of systemic blood and renal venous blood, the latter being withdrawn through a long radiopaque catheter inserted by way of the basilic vein, subclavian vein, superior vena cava, right auricle and inferior vena cava into the renal vein. Since clearance techniques are based on the assumption that the test substance is completely removed from the blood during one circulation through the active renal tissue, renal vein catheterization should serve as a useful refinement of clearance methods applied to human disease.

If the clearance of inulin (glomerular filtrate) and of diodrast (renal plasma flow) are measured simultaneously, the proportion of plasma filtered by the glomerulus, $\frac{C_I}{C_D}$, (filtration fraction) can be determined. If the pressure in the glomerular capillaries increases, the glomerular filtrate and therefore the filtration fraction will likewise increase.

The amount of plasma circulating through the kidney in a given time is determined from the plasma clearance of diodrast. Since the weight of the kidney bears an approximate relation to body surface,

the blood flow per gram of kidney can be calculated This is no sufficient, however, for estimating whether or not renal ischemi exists because in addition to individual variatons in the weight of the kidneys, pathologic processes may have destroyed a certai number of nephrons. Under these circumstances, the blood flow t the nephrons which remain may be adequate although the tota renal plasma flow may be reduced. The functional tubular mass mus therefore be determined Goldring, Chasis, Ranges and Smith (1940 have described the following method for its estimation:

If the concentration of diodrast in plasma is increased, a leve will finally be attained which exceeds the excretory capacity of th tubules. Under these conditions, the diodrast excreted by the tubule (diodrast in the urine minus diodrast by filtration) reaches a constan level which expresses the maximal capacity of the tubules to excret this substance Since this depends upon the activity of the tubula cells, it may be concluded that the maximal excretion of diodras is an expression of the functional tubular mass This value has been called TM_D (tubular mass, diodrast).

The ratio $\frac{C_D}{TM_D}$ expresses, therefore, the plasma flow per unit o functioning tubular tissue. In this way, errors of interpretation due to differences in kidney size of individuals of similar surface area disappear. Under pathologic conditions when nephrons are either inactive or nonfunctioning, study of the C_D may suggest the presence of renal ischemia, but since the tubular mass, TM_D, may likewise be diminished, blood flow per unit of functioning tissue, $\frac{C_D}{TM_D}$, may be normal

The circulation of the kidney has considerable influence on its *functional activity Glomerular filtration depends* mainly on the pressure in the glomerular capillaries When the capillary pressure of the glomerulus falls, as a result, for example, of narrowing of the afferent arteriole, vasoconstriction of the efferent arteriole can compensate for this fall and maintain normal values. In this way the process of filtration (plasma clearance of urea, inulin, etc) remains unaltered, but tubular ischemia is produced, i e , the clearance of diodrast is diminished When tubular function becomes impaired, the power of reabsorption and excretion diminishes which results in poor concentration of the urine and a diminution of the TM_D In

this case, the renal plasma flow falls while the glomerular filtration is maintained and the filtration fraction $\frac{C_I}{C_D}$, increases

Some of the relationships of altered renal function to changes of renal circulation are shown schematically in figure 12.

B) Renal Blood Flow—Renal blood flow in the animal made hypertensive by renal ischemia will now be considered. It would appear at first glance that the amount of blood passing through the kidney must necessarily be diminished in this type of hypertension since the procedure consists of constricting the renal artery. It must be borne in mind, however, that the blood flow through an organ does not depend on any one factor but is determined by the arterial pressure, the resistance offered to the passage of blood by the vessels of that organ, and the venous pressure As regards the kidney, the venous pressure is of little significance in experimental conditions since it remains constant as long as cardiac insufficiency is absent. The renal blood flow will, therefore, depend upon the arterial pressure in the renal artery and upon the resistance to blood flow in the intrarenal arterioles and capillaries One of the most striking characteristics of the renal circulation is its adaptation to changes in arterial pressure The blood flow may remain unaltered despite considerable variations in blood pressure Studies of renal blood flow and of mechanisms concerned in its maintenance have been made possible by the unique distribution of blood vessels in the kidney and by the property of certain substances to be eliminated exclusively by either the glomeruli or the tubules Thus, glomerular filtration depends largely upon the pressure in the glomerular capillary The filtration pressure increases when the arterial pressure increases or when the efferent arterioles constrict Contrariwise, it diminishes when the blood pressure falls or when vasodilatation of the efferent arteriole occurs It appears to have been demonstrated experimentally that in some cases the renal blood flow may remain unchanged after constriction of the renal artery and development of hypertension in dogs This can be explained in two ways: (1) The rise of blood pressure may compensate for the narrowing of the artery so that the pressure in the renal artery distal to the clamp is the same as before operation (figure 12-I). (2) "The autonomic control of the renal vascular bed" may maintain blood flow despite the fall of pressure If the blood flow is maintained by the former mechanism, glomerular filtration

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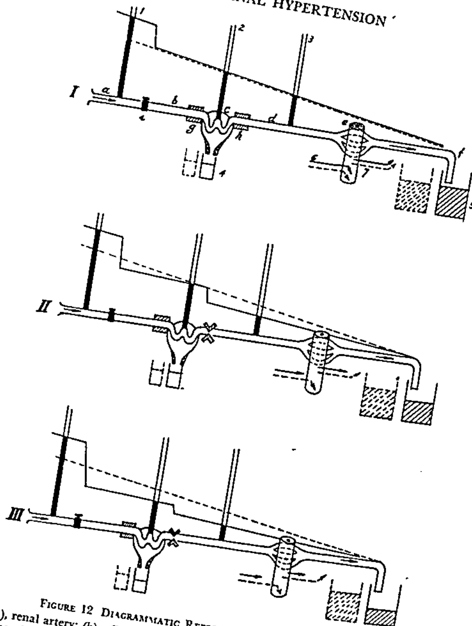


FIGURE 12 DIAGRAMMATIC REPRESENTATION OF A NEPHRON

(a), renal artery; (b), afferent glomerular arteriole; (c), glomerulus; (d), efferent glomerular arteriole, (e), tubule; (f), renal vein· (g) and (h) represent the musculature of the afferent and efferent arterioles; (i), constriction of renal artery by a Goldblatt clamp Vertical columns represent the blood pressure: (1) in the renal artery; (2) in the glomerulus; (3) in the efferent arteriole; the solid line indicates the fall of pressure in the renal vascular system, the dotted line repre-

should not change, while if it is maintained by the latter, glomerular filtration should become reduced.

Levy, Light and Blalock (1938) measured the renal blood flow in dogs before and after renal ischemia and found a decrease of 40 per cent in the hypertensive dogs Pressure in the renal artery distal to the clamp was found to be reduced in all cases. Mason, Robinson and Blalock (1940) used unanesthetized animals with explanted kidneys which allowed them to take the pressure in the renal artery by direct puncture without laparotomy. The pressure in the renal artery in the majority of instances was less than that before constriction of the artery, although there was a tendency for this pressure to rise gradually In one of fifteen cases the pressure in the renal artery was equal to that which existed before the constriction No correlation existed between the pressure in the renal artery and the systemic arterial pressure

Kohlstaedt and Page (1940a), in perfusing isolated kidneys, reported that renin was secreted as a result of reducing pulse pressure without modifying blood flow Since renin is now considered to be the probable chemical mediator of renal hypertension, these experiments would appear to indicate that its production does not depend upon ischemia, although it is frequently associated with it These experiments will be discussed in detail in Chapter VIII

Corcoran and Page (1938) extended these studies and tried to ascertain if it were possible to obtain hypertension by constriction of the renal artery without producing ischemia of the kidney In

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sents the fall of pressure in the normal renal vascular system; (4) glomerular filtrate, (5) renal blood flow Arrows 6 and 7 represent tubular excretion and reabsorption respectively, dotted arrows represent normal values

I Constriction of the renal artery produces hypertension The pressure distal to the clamp is normal and therefore there is no change of glomerular filtration, of tubular excretion and reabsorption, or of renal blood flow

II Constriction of renal artery with hypertension The pressure distal to the clamp has fallen Pressure in the glomerulus, however, is normal due to vasoconstriction of the efferent arteriole Glomerular filtration is normal but the tubule is ischemic so that its capacity to reabsorb and excrete is reduced Blood flow is diminished Filtration fraction increases

III Constriction of the renal artery with hypertension As in the previous case, the pressure distal to the clamp has fallen, but in this case vasoconstriction of the efferent arteriole does not entirely compensate and, therefore, the pressure in the glomerulus is less and the glomerular filtrate becomes diminished producing an increase of nonprotein nitrogen in the blood Changes in tubular reabsorption and excretion are more pronounced Renal blood flow is diminished

investigations carried out with indirect methods of plasma clearance, they showed that moderate elevation of blood pressure could be obtained in the dog by constriction of the renal artery without producing more than transitory changes in the clearance of phenol red and inulin These experiments suggested that neither the renal blood flow nor the intraglomerular pressure were diminished. Their observations were further amplified and confirmed in subsequent studies (Corcoran and Page, 1941a, b, 1942) from which they concluded that it is possible to obtain hypertension by constriction of the renal artery or by compression of the renal parenchyma by perinephritis without constant or persistent changes in the clearances of diodrast, phenol red, inulin, or urea, and, therefore, probably without the existence of ischemia of the renal excretory tissues This has received further support in experiments in which renal blood flow was studied by measuring the percentage extraction of phenol red and of inulin. In view of these findings, Corcoran and Page suggested that diminution of pulse pressure might be the factor responsible for the elevation of blood pressure (see Chapter VIII) Alpert and Thomas (1940) also concluded from their experiments that renal blood flow may remain normal in hypertensive animals

Enger, Linder and Sarre (1938a) and Warthin and Thomas (1943) have given certain support to the conclusions of Corcoran and Page by showing in acute experiments that blood flow rapidly returned to its normal level after constriction of the renal artery by a clamp despite the elevation of blood pressure.

Schroeder and Steele (1940) also studied the behavior of renal blood flow after constriction of the renal artery. They observed that the blood flow returned to its normal level within a few minutes of compression unless the constriction was extreme.

C) The Metabolism of Ischemic Renal Tissue has been the object of considerable investigation Mason, Evers and Blalock (1937) found that the renal venous blood was no more reduced in hypertensive dogs with explanted kidneys than in normal dogs. Levy, Light and Blalock (1938) confirmed this finding by showing that the arterio-venous oxygen difference of the kidney was not significantly altered in hypertensive dogs Since these animals showed a 40 per cent reduction of renal blood flow, it may be concluded that the consumption of oxygen by the kidney was reduced to a similar degree Mason, Evers and Blalock (1937) concluded that these results might indicate (1) a

reduction of kidney metabolism, (2) a reduction in the amount of functioning tissue, or (3) the presence of vascular changes interfering with oxygen diffusion.

In normal kidneys, Glaser, Laszlo and Schurmeyer (1933) and Van Slyke, Rhoads, Heller and Alving (1934) found a linear relation between oxygen consumption and renal blood flow. Levy, Mason, Harrison and Blalock (1937) observed a reduction of blood flow and of oxygen consumption in kidneys with occluded ureters It should be pointed out that the kidney may well react to ischemia by reducing its oxygen consumption since it is an organ having a venous oxygen saturation of 85 per cent (Van Slyke, Rhoads, Heller and Alving, 1934, Levy Light and Blalock, 1938).

Studies of the oxygen consumption of slices of renal tissue by Warburg's method have given contradictory results According to Gerbi, Rubenstein and Goldblatt (1940), the oxygen consumption of ischemic renal tissue was reduced in rabbits Raska (1943) found that ischemic kidney tissue of hypertensive dogs had a diminished oxidative capacity as indicated by oxygen consumption and by ammonia production in the presence of amines and amino acids

Mason, Robinson and Blalock (1940), on the other hand, found no differences in the oxygen consumption of kidney slices in dogs Attributing the results of Gerbi and collaborators to the presence of necrotic tissue in the kidney slices employed, they concluded that reduction of oxygen consumption was not an essential characteristic of the kidney of a hypertensive animal

Cruz Coke, Niemeyer and Fernandez-Popelacre (1944) found that the oxygen consumption without substrate was the same in normal and ischemic rat kidney but that in the presence of 0 01 M lactic acid or 0 01 M succinic acid, it was less in the ischemic kidney

Certain differences between ischemic and normal tissue have been demonstrated in studies of several enzyme systems of the kidney Dicker (1937a) found that the ischemic kidney had less invertase action and less ability to reduce methylene blue than the normal kidney Studies concerning decarboxylation and deamination of the ischemic kidney will be described in Chapter XI

D) Excretory Function of the kidney has received considerable attention If both renal arteries are markedly constricted, or if only one is similarly constricted and the other kidney removed, a rise of blood pressure ensues together with a retention of urine, nonprotein

nitrogen, creatinine and guanidine, and a marked reduction of the plasma clearance of urea and of the excretion of phenolsulphonphthalein (Goldblatt, Lynch, Hanzal and Summerville, 1934). Some animals develop convulsions, hypertension, and not infrequently separation of the retina by exudates or hemorrhages. Death may occur a few days after the operation (Fasciolo and Cramer, 1938). We will return to this convulsive uremia later. Other animals survive for longer periods and present a picture of asthenia, weight loss, anorexia, and terminal coma. Vomiting, gastro-intestinal hemorrhage, and marked elevation of blood urea or nonprotein nitrogen occur at times. This resembles the syndrome of true uremia.

If the renal arterial constriction is moderate or carried out in stages, permanent hypertension may be obtained without changing renal excretory function as indicated by normal blood levels for nonprotein nitrogen, urea, creatinine, and guanidine,[2] by the normal excretion of phenolsulphonphthalein;[3] and by normal clearances of urea, inulin, phenol red, and diodrast (Goldblatt and collaborators, 1934; Corcoran and Page, 1941a, b, 1942; Alpert and Thomas, 1940) These findings indicate that hypertension from renal ischemia can be produced without changing gross excretory function of the kidney.

Between the two extremes of renal function mentioned, that is to say, that which is incompatible with life and that which can not be revealed by the most delicate tests, all stages of transition exist. Two types of hypertension can be obtained by Goldblatt's method. The first is one of benign hypertension with or without slight renal insufficiency, and the second is accompanied by pronounced renal insufficiency, and by anatomic lesions characteristic of the malignant stage. This will be discussed later.

EXTRARENAL CHANGES. *E). Hemodynamic Changes.*—Both systolic and diastolic blood pressures have been determined with precision by the use of oscillatory and auscultatory techniques (Collins, 1936; Wood and Cash, 1936; Freeman and Page, 1937), and

[2] Goldblatt, Lynch, Hanzal and Summerville, 1934; Page, 1935a; Elaut, 1936a, b; Collins, 1936; Dicker, 1938, Gibson and Robinson, 1938, Fasciolo, 1939, and others

[3] Goldblatt, Lynch, Hanzal and Summerville, 1934; Elaut, 1936a, b, Collins, 1936, Gibson and Robinson, 1938; Dicker, 1938

better still by the use of the optical manometer of Hamilton (Fasciolo, 1939; Katz, Friedman, Rodbard and Weinstein, 1939). Elevations of both systolic and diastolic pressure have been found regardless of the method utilized

The *pulse rate* remains essentially unchanged.

The *minute volume output* of the heart was studied by Holman and Page (1938) in dogs before and after the production of hypertension The minute volume output was determined by the Fick principle which depends upon measuring oxygen consumption and the arterio-venous oxygen difference. The mixed venous oxygen sample was obtained by puncture of the right ventricle. No significant changes in cardiac output were observed when the animals became hypertensive

The *pulmonary artery pressure* was measured by Katz and Steinitz[4] in dogs before and after the production of hypertension Using a laborious method based on the principle of London's cannulas, they measured the pressure without resorting to thoracotomy or anesthesia Average readings of 28 mm. Hg systolic and 11 mm. Hg diastolic were obtained in both normal and hypertensive animals indicating clearly that the pulmonary vessels do not participate in the vascular constriction of this type of hypertension.

The *blood volume* of hypertensive dogs was determined by Freeman and Page (1937) and by Gibson and Robinson (1938) using Evans blue dye, T 1824 No significant variations were found. The blood volume of rats made hypertensive by subtotal nephrectomy was studied by Beckwith and Chanutin (1941) who found certain changes in the plasma and red cell volume but no significant differences in total blood volume According to Griffith and Ingle (1940) the posterior pituitary may play some rôle in the changes of blood volume which they observed

Composition of the Blood of hypertensive animals has received considerable attention We have already referred to the renal function of these animals. We must repeat that if constriction of the renal arteries is excessive, the resultant hypertension is accompanied by renal insufficiency characterized by a retention of substances in the blood and by the appearance of abnormal elements in the urine. This picture is too well known to be described here. Since hyper-

[4] Steinitz and Katz, 1939, Katz and Steinitz, 1940

tension without excretory insufficiency of the kidney can be obtained, however, it is of interest to consider the studies which have been performed in this type of hypertension with regard to blood changes

The hydrogen ion concentration of the venous blood was studied potentiometrically by Muller and Nickel (1940), who found an average pH of 7 32 in hypertensive dogs. This was essentially the same as in normal controls.

Page (1935a) observed no significant changes in the lipid and protein content of plasma except for a slight increase of free cholesterol at the expense of the esterified fraction.

The guanidine group of substances is of special interest because they are retained in renal insufficiency Since they also possess a pressor action, it has been postulated that they may play an important rôle in human hypertension (see Chapter XI) From the literature it may be concluded that although the guanidine concentration of plasma increases when renal excretory insufficiency appears, hypertension may occur without any increase in its concentration (Goldblatt, Lynch, Hanzal and Summerville, 1934, Child, 1938b, Helmer and Page, 1938, and Major, Weber and Rumold, 1939).

Eichelberger (1943) observed a redistribution of water in skeletal muscles of dogs with experimental renal hypertension which indicated that an extracellular edema existed.

Studies concerning tyramine are discussed in Chapter XI

Vasomotor Reactions —One of the interesting problems in renal hypertension is that concerning the functional state of the nervous regulators of blood pressure. The carotid sinus and cardioaortic nerves are incapable of maintaining blood pressure within normal limits once the kidney has become ischemic. According to Bouckaert, Elaut and Heymans (1937) and Grimson (1939), occlusion of the carotids produces only slightly greater rises of blood pressure in hypertensive than in normal dogs. Verney and Vogt (1938) did not find appreciable differences Goldblatt, Kahn, Bayless and Simon (1940) showed that removal of both carotid sinuses did not modify the development of hypertension produced by renal ischemia, nor was the level of pressure reached by the hypertensive animals different from that of normals

The pressor regulator system, therefore, appears to be actively functioning in renal hypertension, but whether it is more or less active than normal is not entirely clear. The evidence suggests that it functions normally at a higher level

The pressor response to various substances has also been investigated in hypertensive dogs The significance of these studies will be discussed in greater detail later and will be mentioned here only in passing. Verney and Vogt (1938) found that some hypertensive dogs are more sensitive than normal to the pressor action of adrenalin and that the injection of tyramine consistently produces a greater rise of pressure in the hypertensives than in the controls. Brown and Maegraith (1941b) confirmed these findings in rabbits. They also found that the pressor response to extracts of the posterior lobe of the pituitary were exaggerated while those to acetylcholine were diminished in rabbits made hypertensive by constriction of the renal artery or by glomerulonephritis produced with nephrotoxic serum

Brown and Maegraith (1941a) were unable to demonstrate that the hypersensitivity of hypertensive animals to adrenalin, tyramine and pitressin was due to a diminished destruction of these substances in the body Ogden, Brown and Page (1940) found a greater sensitivity to pitressin during the pre-hypertensive phase in rabbits Katz and Friedberg (1939) injected Fourneau 933 into unanesthetized dogs in sufficient amount to invert the action of adrenalin In normal and hypertensive dogs, Fourneau 933 produced quantitatively the same fall of pressure accompanied by tachycardia, diminution of pulse pressure, salivation, sweating, and so forth These authors concluded that the hypertensive substance was not sympathomimetic (see Chapter VI) Robbers and Westenhoeffer (1939) obtained no fall of pressure from cocaine in eight dogs made hypertensive by ligation of one renal artery From this they concluded that tyramine can not be the cause of renal hypertension Friedberg and Katz (1939) found similar responses to renin and adrenalin in normal and hypertensive dogs

Leiter and Eichelberger (1939), and Page and Helmer (1940b), on the other hand, found a greater response to renin in hypertensive dogs Leiter and Eichelberger (1943) observed that the intravenous injection of renin produced rises of similar degree and duration in unanesthetized normal and renally abnormal dogs. Such renal abnormalities as ischemia and constriction of the ureter were employed After stopping repeated or continuous injections of renin, on the other hand, they showed that the pressor effect was maintained for a much longer time in the hypertensives than in the normal controls Kapp, Friedland and Landis (1941) injected kidney extracts heated to 55° to 56°C for 20 minutes The increases in

pressure were slightly greater in hypertensive rabbits than in the normal controls except when the dosage of extract was very great, in which case the response was maximal and was equal in both groups

Page (1941a) studied this point in a larger number of dogs before and after producing hypertension, and concluded that the responses to renin were somewhat greater after the development of hypertension while those to hypertensin were the same. He interpreted the results as being due to a greater amount of "renin-activator" (hypertensinogen) supposedly present in the hypertensives (see Chapter V). In some cases, the response to angiotonin was also greater.

The greater sensitivity of hypertensive animals to tyramine, renin and pitressin appears to be definite. As yet, however, the cause of this phenomenon remains to be elucidated.

The action of hypertensin is potentiated by tyramine (unpublished observations) (see figure 56b). This might perhaps be explained by the greater sensitivity of hypertensive animals to this substance

It would be of interest to know if a previous injection of renin in small amounts produces an increased sensitivity to tyramine, pitressin, and perhaps to renin and hypertensin.

The behavior of dogs before and after the production of renal hypertension has been studied in regard to the "cold pressor test" of Hines and Brown (1933). According to Thomas and Warthin (1940) the responses are normal in 89 per cent of the cases before the hypertension and are essentially the same after hypertension has been produced.

CHANGES OF BLOOD PRESSURE FROM INTERCURRENT CAUSES. Intercurrent diseases are apt to produce falls of blood pressure in hypertensive dogs. According to Levy and Blalock (1938), Katz, Friedman, Rodbard and Weinstein (1939) and Wakerlin and Gaines (1940), distemper produces a fall of pressure which returns to its initial level as the infection disappears. Our observations are in agreement with these findings Levy and Blalock (1938) have also observed that the administration of typhoid vaccine and other pyrogens produces a transitory fall of pressure in hypertensive dogs. These results may perhaps be explained at least in part by the studies of Chasis, Goldring and Smith (1942), who observed that the

administration of pyrogens to human beings produced marked renal hyperemia This subject is considered in greater detail in Chapter XVI. The effect of pregnancy on the course of renal hypertension is discussed in Chapter X.

INFLUENCE OF DIET ON RENAL HYPERTENSION

Chanutin and collaborators[5] carried out an extensive study of the action of protein diets on the kidney and systemic circulation of the rat The diets employed contained different percentages of protein varying from 10 to 80 per cent The proteins administered consisted of whole meat, extracted meat, whole liver and extracted liver. In normal rats, renal hypertrophy developed which was proportional to the amount of protein in the diet, but no rise of blood pressure occurred. In rats with subtotal nephrectomy, the incidence of hypertension was greater in the animals treated with the extract of whole meat. In dogs with hypertension from renal ischemia, Verney and Vogt (1938) studied the effect on blood pressure of imposing an excretory burden on the kidney Rises of blood pressure were obtained by administering sodium chloride, meat or urea Sodium chloride produced the greatest rises while meat and urea had a similar but less pronounced action This effect was abolished by changing the diet, and did not occur in normal animals or in those with subtotal nephrectomy. Cash and Wood (1938), using meat diets, observed similar rises when the diet produced an increase of body weight Maclachlan and Taylor (1940) observed that in a dog a meat diet not only intensified the hypertension but also produced cerebral symptoms and separation of the retina This effect was repeated several times. Furthermore, the daily administration of 50 gm. of urea was just as effective as meat Philipsborn, Katz and Rodbard (1941), on the other hand, were able to obtain this elevation in only 2 of 14 dogs studied. Goldblatt, Kahn and Lewis (1942), using dogs, and Grollman, Harrison and Williams (1940a), using rats, likewise observed no rise of pressure from meat diets or from salt Guerrant, Scott and Wood (1943) recently noted no significant increases of blood pressure from the ingestion of meat diets or from the administration of urea to hypertensive dogs Alpert and Thomas (1943) likewise observed

[5] Chanutin, 1931, Chanutin and Ludewig, 1936a, b, c, 1939a, b, c

no change of blood pressure in 2 dogs with renal hypertension, with neurogenic hypertension, and 1 with normal blood pressu as a result of varying the protein intake.

That high protein diets are capable of producing renal changes i the rabbit was observed by Newburgh (1919) and Newburgh an Clarkson (1923) and confirmed by Nuzun, Osborne and Sansu (1925), Nuzun, Seegal, Garland and Osborne (1926); and Anderso (1926). Nuzun and collaborators reported the development of hype tension in these animals, but Anderson observed none even in an mals in which a high protein diet was combined with reduction o renal mass In the rat, Newburgh and Curtis (1928), Newburgh an Johnson (1931), and Blatherwick, Medlar, Connolly and Bradsha (1931) observed renal changes with diets rich in proteins from differ ent sources Alpert and Lilienthal (1943) noted no significant an atomic changes from the administration of high protein diets t normal dogs and dogs with renal and neurogenic hypertension Mitchell (1929) and Bischoff (1932) have discussed the older liter ature on the effect of high protein diets on the kidney. Van Slyke Rhoads, Heller and Alving (1934) observed that high protein diets were capable of producing a considerable increase of renal blood flow in normal dogs Alpert and Lilienthal (1943) found that diodrast, inulin, and urea clearances became higher in dogs on a high protein diet Pitts (1944) noted an increased renal blood flow and filtration rate, a normal filtration fraction, and a decrease in the total renal resistance largely due to the vessels on the efferent side of the glomerulus following the administration of high protein diets to dogs

It may be concluded that it has not been definitely demonstrated that diets rich in protein are capable of exaggerating renal hypertension Taking into account, however, the importance of the kidney in the elimination of products of protein catabolism, it is possible that these diets modify to some extent the evolution of renal hypertension

Calder (1942) reported that he had observed an elevation of blood pressure in rats from the administration of diets partially deficient in the thermostable complex of the vitamin B group, whereas those that received diets deficient in all of the vitamins of the B group showed a slight hypotension More recently, Calder (1944) described the

renal pathology in these deficient rats as similar to changes in the human kidney in cases of essential hypertension Martin (1913) reported that a diet with 5 to 10 per cent tyrosine produced hypertension in rats Honorato and Vadillo (1911) obtained no change of blood pressure in white rats from the administration of a choline-free diet

PATHOLOGY

In considering the anatomic lesions of animals with renal ischemia, the type of hypertension studied must be borne in mind Three distinct groups must be considered (1) those animals with moderate constriction of the renal artery, in excellent general condition, and without the slightest sign of renal insufficiency, (2) those with more severe renal ischemia with obvious changes in renal function leading to death within a few weeks with a typical picture of malignant hypertension; and (3) those which survive after an acute period of renal insufficiency but show some impairment of the excretory capacity of the kidney This division is important since the pathologic pictures are quite different in each case In the first group, as we shall see later, there is characteristically a lack of pathologic lesions. The second, however, is associated with pronounced changes in the vascular tree These are of recent origin since the rapidity of the process precludes the development of chronic lesions In the third group, the lesions are predominantly cicatricial although acute vascular lesions may coexist

GROUP A —BENIGN HYPERTENSION In benign hypertension, the lesions found are quite insignificant even in animals in which the hypertension is of long standing Macroscopic study of the circulatory system reveals a moderate degree of cardiac hypertrophy after the hypertension has persisted for some time (Flaut, 1936b; Collins, 1936; Gibson and Robinson, 1938) The large vessels show no changes and the aorta is of normal thickness (Collins, 1936). Microscopically, there is hypertrophy of the media of the arterioles of various organs, especially skeletal muscle (Goldblatt, Lynch, Hanzal and Summerville, 1934, Elaut, 1936a, b, and others) Lesions of the retinal arterioles will be considered later

There is slight thickening and adherence of the renal capsule (Goldblatt, Lynch, Hanzal and Summerville, 1934), slight diminu-

tion in the size of the kidney and an increase of the collateral circulation (Elaut, 1936a, b; Collins, 1936, and others). Microscopically there may be a complete absence of lesions or a slight atrophy of the tubules according to the degree of the ichemia (Goldblatt and collaborators, 1934; Elaut, 1936a, b; Collins, 1936)

Up to this point we have considered only those studies which have been carried out in dogs in which renal function has been measured with appropriate methods Findings in other species resemble more closely the malignant type of hypertension which will be described later.

Elaut (1936a, b) first called attention to minor changes in the juxtaglomerular apparatus in dogs with benign hypertension produced by renal ischemia. This was subsequently confirmed and these lesions have also been shown to be present in animals with malignant hypertension Since importance has been attached to these observations in relation to the interpretation of the mechanism of renal hypertension, we will discuss the present status of our knowledge concerning this apparatus and its changes.

In the year 1925, Ruyter observed that the afferent arteriole of the glomerulus in its juxtaglomerular portion in rats was made up of one or several layers of nonfibrillary cells rich in granules, which he identified as epithelioid cells. Smooth muscle fibers were lacking at this point so that the epithelioid cells rested directly on endothelium. Ruyter suggested that these cells might be concerned in the regulation of the glomerular blood flow. Later, Oberling (1927) and Goormaghtigh (1932) described epithelioid cells of a similar nature in human kidneys. Zimmermann (1933) observed that as the afferent arteriole approached the glomerulus in mammalian kidneys, there was a multiplication of the cells of the medial layer which enveloped the arteriole and part of the glomerulus like a sleeve. He gave the name *"polkissen"* to this formation in virtue of its appearance. Another characteristic described by Zimmermann was the appearance of the intermediate segment of the distal tubule where it came in contact with the afferent arteriole. Here the epithelial cells changed in form, becoming higher, and their nuclei became closely grouped together, from which the term *macula densa* was derived.

There is considerable disagreement among investigators concerning the nature of the cells of the juxtaglomerular apparatus as regards

both origin and function. For further details we refer the reader to Smith (1940) who has reviewed this subject in detail. The recent publication of McManus (1942) should also be consulted

Goormaghtigh and Grimson (1939) and Goormaghtigh (1939a, 1940a, b) came to the conclusion that renal ischemia in dogs and rabbits produced a proliferation and hypertrophy of the afibrillar cells of the juxtaglomerular apparatus, transformation of fibrillar into afibrillar cells, and increase in the granulation of these cells They also observed changes in the macula densa Goormaghtigh and *Handovsky (1938) observed hypertrophy of the juxtaglomerular* apparatus in dogs made hypertensive by excessive doses of calciferol These findings have been interpreted as indicating the existence of a true gland of internal secretion located in the wall of the afferent arteriole of the glomerulus Dunihue and Candon (1940) and Dunihue (1941) observed hypertrophy and hyperplasia of the granular cells in rabbits when hypertension was produced by cellophane perinephritis Graef and Smith (1940) likewise observed that renal ischemia produced hyperplastic, hypertrophic and metaplastic changes of the epithelioid cells of the juxtaglomerular apparatus although they emphasized that many individual variations existed even in normal kidneys. Goldblatt, on the other hand, has not observed characteristic changes (personal communication). Oberling (1944a, b) rejected Goormaghtigh's hypothesis relating the juxtaglomerular apparatus to hypertension because of technical difficulties in making reliable comparisons of hypertensives to normals and because the juxtaglomerular apparatus tended to degenerate and disappear as hypertension progressed

GROUP B—MALIGNANT HYPERTENSION (ACUTE LESIONS) This type of hypertension is observed in animals in which the renal artery is constricted to an extreme degree The blood pressure rises rapidly, the general condition of the animal is precarious, and obvious renal insufficiency is frequently present. Vomiting, melena, and blindness produced by detachment of the retina or retinal hemorrhages often occur In extreme cases convulsions may appear and the animals may die in a comatose state. A few hours before death, the blood pressure falls

There is general agreement as regards the macroscopic and microscopic lesions present. Concerning the mechanism of production



FIGURE 13 PETECHIAL HEMORRHAGES IN EXPERIMENTAL MALIGNANT HYPERTENSION

Section of abdominal wall showing the peritoneal surface Subperitoneal punctate hemorrhages are seen (After Fasciolo, 1939).



FIGURE 14 VISCERAL HEMORRHAGES

mitral valve, hemorrhage is extensive

of these lesions, however, there is a certain amount of controversy.

Lesions have been observed in the dog by Goldblatt (1938a), Child (1938b), Verney and Vogt (1938), Fasciolo (1939), and Winternitz and Waters (1940), in rabbits by Drury (1938) and Wilson and Pickering (1938); and in rats by Wilson and Byrom (1939), Díaz and Levy (1939) and Schroeder and Neumann (1942).

Macroscopic Study.—Vascular changes consisting of petechiae, hemorrhages, and in some cases exudation, are easily observed macro-



FIGURE 15 MICROSCOPIC APPEARANCE OF THE HEMORRHAGES

Interstitial hemorrhages in the heart of a hypertensive dog Hemalum Eosin (After Fasciolo, 1939)

scopically The distribution and severity of these lesions vary in different species Subperitoneal punctate hemorrhages are frequently seen. In the small intestine they occur particularly along the mesenteric border and on the mesentery itself In the intestine and stomach, submucous hemorrhages are frequently observed which in some cases are so pronounced that the intestinal lumen contains blood. In the pancreas, subserosal and parenchymatous petechiae are encountered In some cases, large hemorrhages occur in the bladder, esophagus, adrenal, gonads, brain, and so forth Under the parietal

peritoneum (*figure 13*) small petechiae may be observed. In the heart, subendocardial hemorrhages are located especially along the papillary muscles of the left ventricle (figure 14). They tend to become confluent and extend deeper and take on the characteristics of a hemorrhagic infarct (figure 15). Hemorrhages within the walls of the large vessels, such as the pulmonary artery, aorta, and large veins, have also been observed.

These acute arterial lesions are frequently found in the eyegrounds



FIGURE 16 OCULAR HEMORRHAGES

Hemorrhages may be seen on the anterior surface of the iris in a dog with hypertension from renal ischemia (After Fasciolo and Cramer, Rev. Soc. argent de biol, 1938, *14*, 393).

(Fasciolo and Cramer, 1938; Verney and Vogt, 1938; Child, 1938b, Cramer. 1940) In the dogs of Fasciolo and Cramer, the retinal changes appeared 8 to 15 days after constricting the renal artery by which time the pressure had undergone a pronounced rise. The lesions observed were iritis, hemorrhages, and separation of the retina. The iritis consisted of inflammatory lesions between the iris and anterior surface of the lens which was followed by the development of synechiae in one animal that subsequently improved. Hemorrhages were seen in the anterior and posterior chambers (figure 16). These were at times small and punctate, and at others so large as to fill the vitreous and obscure the fundus. Partial or complete separation

of the retina occurred. The retina was raised by a homogeneous gelatinous-like substance (figure 17). Large serous effusions of 300 cc. or more have been described in the pericardial and peritoneal cavities (Fasciolo, 1939).

Macroscopic changes in the kidney depend upon the duration of the ischemia Following pronounced constriction of one renal artery, the clamped kidney becomes atrophic and fibrous. The capsule is adherent, the surface is grossly granular, and on section the kidney is tough and fibrous Renal function may be very poor. Maintenance of excretory function by the normal kidney prevents the development of the general picture of malignant hypertension. One curious fact,

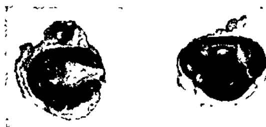


FIGURE 17. SEPARATION OF THE RETINA IN A DOG WITH EXPERIMENTAL RENAL HYPERTENSION

Antero posterior section of an eye Note that the retina is separated and raised by a substance of gelatinous consistency (After Fasciolo and Cramer, Rev Soc. argent. de biol, 1938, *14*, 393)

the significance of which is discussed below, is a lack of acute vascular lesions, petechiae, and hemorrhages in the ischemic kidney (Goldblatt, 1938a, and Child, 1938b, in dogs, Wilson and Pickering, 1938, in rabbits; and Wilson and Byrom, 1939, in rats) Schroeder and Neumann (1942), on the other hand, did observe these changes in rats.

Microscopic Study.—Microscopic study of the organs reveals even in the absence of macroscopic lesions, degenerative changes of variable degree in the arterioles consisting of hyalinization and necrosis In some arterioles, hyaline material is deposited immediately beneath the endothelium which remains intact This deposit may be located eccentrically or concentrically, may not impinge upon the lumen of the vessel at all, or may obliterate it partially or even completely

(plate 1). At times, the wall of the arteriole may be necrosed. Serial sections of an artery may show it to be relatively normal in one part, partially or completely hyalinized in another, or completely necrosed in still another (Goldblatt, 1938a). There is neither a reduplication of the elastica nor proliferation of the intima (Goldblatt, 1938a; Wilson and Pickering, 1938).

It is not always possible to detect the site of origin of the hemorrhages. They may be due to rupture or to leaks along the wall of the necrosed arterioles In some cases they can be attributed to capillary lesions. The distribution of the arteriolar lesions is the same as that described in the macroscopic section. Some structures appear to be undamaged Goldblatt (1938a) found only slight hyalinization of the intima without necrosis in skeletal muscles Pulmonary lesions are confined to bronchial arterioles. The branches of the pulmonary artery remain unaffected. There are likewise no arteriolar changes in the ischemic kidney Wilson and Pickering (1938) and Wilson and Byrom (1939) found no lesions of necrotizing arteritis and arteriolitis in the skin, striated muscle, and ischemic kidney of rats and rabbits Wilson and Pickering (1938) found that in rats with permanent hypertension from unilateral renal ischemia it was possible to observe fibrinoid and hyaline degeneration and necrosis

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PLATE 1 ARTERIAL LESIONS IN MALIGNANT HYPERTENSION

Figure 1 Arteriole in submucosa of large intestine. Beginning subendothelial deposit of hyalin Endothelium well preserved Hematoxylin and Eosin ×265

Figure 2 Arteriole in submucosa of stomach Obliterative hyalinization of intima, endothelium still recognizable but nuclei reduced in number and pyknotic Hematoxylin and Eosin ×430

Figure 3 Arteriole in submucosa of small intestine Lumen completely obliterated by accumulation of hyalin containing a few pyknotic nuclei Hematoxylin and Eosin ×430

Figure 4 Arteriole in submucosa of stomach Portion of entire thickness of wall necrotic Normal thickness of wall and lumen natural size Hematoxylin and Eosin ×325

Figure 5 Arteriole, cut longitudinally, in submucosa and mucosa of large intestine. Partly hyalinized, partly necrotic, with extravasated blood around it. A portion of the same arteriole, in the submucosa, immediately proximal to the part included in this figure, was entirely normal Hematoxylin and Eosin ×255 (After Goldblatt, J Exper. Med, 1938, *67*, 809)







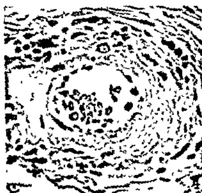




PLATE I

of the arterioles and capillaries with proliferation of the intima and fragmentation of the elastica in the nonischemic kidney. No vascular lesions, however, were observed in the ischemic kidney Hemorrhages within the walls of the arteries were found.

Changes in the histology of the kidney depend upon the duration and degree of ischemia as was mentioned in the macroscopic section. Tubular atrophy and degeneration or complete necrosis of the kidney may be observed Connective tissue proliferation occurs in the atrophic kidney.

Pathogenesis of the arterial lesions—Since the arteriolar lesions *just described appear in hypertensive animals with renal insufficiency,* Goldblatt (1938a) suggested that two factors were involved in their production—a mechanical factor, the arterial hypertension, and a humoral factor, renal insufficiency The following findings support this interpretation Bilateral nephrectomy produces nitrogen retention without necrotizing arteriolitis These arteriolar lesions do not appear in cases of benign hypertension even of long duration. The absence of arteriolar lesions in the ischemic kidney is, according to Goldblatt, a further proof in the sense that in this case the application of the clamp prevents the development of hypertension in the vessels distal to the clamp The renal vessels would, therefore, be *protected from the elevation of blood pressure*

In order to verify this hypothesis, Goldblatt and Kahn (1940) constricted one renal artery markedly and ligated the ureter of the opposite kidney in dogs In this way they produced hypertension with renal insufficiency in dogs with only one ischemic kidney. The vascular lesions described above were present in various organs as well as in the kidney with the ligated ureter but not in the ischemic kidney. Control animals with ligation of only one ureter developed neither hypertension, renal insufficiency, nor arteriolar lesions In addition, renal insufficiency produced by uranium nitrate in animals with benign hypertension, was accompanied by fibrinoid arteritis, *arteriolar necrosis, hemorrhages, and petechiae*

The lack of macroscopic and microscopic changes in the ischemic kidney of animals with malignant hypertension has been confirmed by Child (1938b) in dogs, Goldblatt (1937b) in monkeys, Wilson and Pickering (1938) in rabbits, and Wilson and Byrom (1939) in rats The latter investigators found that it was possible to produce persistent hypertension in rats by constriction of one renal artery

only, leaving the other kidney intact. The animals frequently developed convulsions, weakness, and coma, which were curable by removal of the ischemic kidney The blood urea nitrogen was normal or increased. The vascular lesions of malignant hypertension were present but not in the ischemic kidney. In the opposite intact kidney, however, hemorrhages and subcapsular petechiae, hyaline and fibrinoid degeneration of the arteries and arterioles, proliferation of the intima, and necrosis of the walls were observed. Fibrinoid degeneration or necrosis of the capillaries occurred in the glomeruli. Since these animals had one normal kidney and since in some of them the blood urea nitrogen was not elevated, the authors concluded that excretory insufficiency of the kidney was not necessary for the production of this type of lesion. In this connection, our observations (Fasciolo and Cramer, 1938) on the production of acute retinal lesions are pertinent. These lesions appeared in some animals without any increase of blood urea nitrogen. In one animal with unilateral ischemia and normal blood urea nitrogen, bilateral separation of the retina and iritis were observed

Wilson and Byrom (1939) believed that the production of arteriolar lesions was not dependent upon renal function but rather upon the combined effect of hypertension and vasoconstriction. Goldblatt and Kahn (1940), on the other hand, insisted that the measurement of blood urea nitrogen was not a sufficient criterion for estimating the state of renal function They assumed that rats which developed malignant hypertension suffered from disturbances of the non-ischemic kidney, probably hydronephrosis which is frequent in the rat, and, therefore, that the results of Wilson and Byrom (1939) were similar to those obtained by them in dogs in which the ureters of the opposite kidney were ligated (Goldblatt and Kahn, 1940).

Recent studies of Winternitz and his collaborators have thrown new light on the production of the arteriolar lesions. In the dog, bilateral nephrectomy caused death generally within seven days of the operation (Winternitz, Mylon, Waters and Katzenstein, 1940). The arterial pressure was little changed and at autopsy few lesions were observed beyond slight edema of the tissues and occasionally subendocardial hemorrhages, valvular and visceral hemorrhages, and focal necrosis of cardiac muscle and of arterial walls. Ligation of both renal arteries caused death within three to four days at the most. Autopsy revealed in these animals hemorrhagic lesions with a

distribution similar to that found in malignant hypertension as described above Furthermore, there was edema and necrosis of cardiac muscle, of the smooth muscles of the walls of the vessels, and of hollow organs Ligation of both ureters produced a similar anatomic picture except that in both kidneys there were pronounced necrotic lesions in the glomeruli

These experiments suggest that the absorption of breakdown products from the kidney which has become necrotic as a result of ligation of the renal artery, may be the cause of the earlier death of these animals as well as the cause of the extensive vascular lesions produced In order to clarify this point, Winternitz, Mylon and Katzenstein (1941b) injected renal extracts into animals previously nephrectomized and obtained a pathologic picture similar to that of dogs with ligation of the renal arteries The substance responsible for the necrosis and hemorrhages appeared to be a protein and although it was not possible to obtain a complete separation, they observed a dissociation between the pressor principle, renin, and the necrotizing action Furthermore, the injection of extracts of testicles into nephrectomized dogs produced extensive arteriolar necrosis which they observed even in the cerebral vessels (Winternitz, Katzenstein, Mylon, Murphy and Zimmermann, 1941) Durlacher and Winternitz (1942) also observed focal necrosis of the myocardium following injection of renal extracts into nephrectomized dogs. Goldblatt (1945b) injected one to five units of crude or moderately purified renin into dogs over a period of three years or longer without producing arteriolar necrosis

In the interpretation of these results, account must be taken of the action of tissue extracts on the coagulation of blood Winternitz, Mylon and Katzenstein (1941a) observed extensive thrombosis as the result of the injection of different extracts, especially those of testicular origin Leiter and Eichelberger (1942, 1943) observed that injections of pig renin into dogs with various renal abnormalities accelerated the production of hemorrhages and necrosis in different parts of the body In animals with normal kidneys, no lesions were observed

In considering the pathogenesis of the arteriolar lesions of malignant hypertension, the following points arise According to Goldblatt, their production depends upon two factors—renal insufficiency and arterial hypertension If we admit that the lesions observed by

Winternitz and collaborators, resulting from the injection of different extracts, are identical with those of malignant hypertension, it is evident that the hypertensive factor is not necessary. Furthermore, Winternitz, Katzenstein, Mylon, Murphy and Zimmermann (1941) were able to produce these lesions in normal dogs. This was confirmed by Leiter and Eichelberger (1942). These different points of view may perhaps be reconciled by assuming that the three factors mentioned, that is to say, renal insufficiency, hypertension (vasoconstriction), and tissue autolysis, are capable of producing capillary and arteriolar changes The existence and severity of the vascular lesions would depend upon the association of two or more of the causative factors The vascular changes would, therefore, not be specific but would be attributable to several processes having the common property of being highly irritative to the vessels

GROUP C—INTERMEDIATE FORMS. In some animals the renal artery may be constricted so as to produce irreparable renal lesions with varying degrees of renal insufficiency but compatible with long survival Changes in function vary with the degree of ischemia and may be characterized by only slight reduction in the clearance of various substances (urea, creatinine, inulin, and so forth) or, in severe cases, by azotemia.

In these cases the vascular lesions are minimal. If renal insufficiency does not exist, hypertrophy of the muscularis of arterioles is the only finding If renal insufficiency is considerable, lesions of malignant hypertension may appear. Hyalinization and necrosis appear to be more pronounced and more widespread in animals with benign hypertension of long duration (Goldblatt, 1938a)

Renal hypertension produces atheromata in the aorta of rabbits (Dill and Isenhour, 1942) Cardiac hypertrophy, predominantly left sided, is frequent in most animals such as dogs, rats, and rabbits (Elaut, 1936a, b, Collins, 1936; Gibson and Robinson, 1938; Chanutin and Ludewig, 1936a; Díaz and Levy, 1939; Schroeder and Neumann, 1942b; Gómez-Salazar, 1942; Pickering and Prinzmetal, 1938b; and others)

Changes in the kidney are characterized by reduction in its size, thickening and adherence of its capsule, and increase in its consistency. Microscopically, there is interstitial fibrosis and tubular atrophy and degeneration. Hyaline degeneration, fibrosis, and re-

ticulosis is found in some glomeruli (figures 18 and 19) (Goldblatt, 1938b; Child, 1938 b; Fasciolo, 1939; Wilson and Byrom, 1939, 1941; and others). Along with these chronic lesions, acute necrotic and hemorrhagic changes may appear if the process becomes malignant. Wilson and Byrom (1939) observed that constriction of the artery of one kidney in rats produced lesions in the opposite kidney. These lesions appeared to be capable of producing chronic changes in that

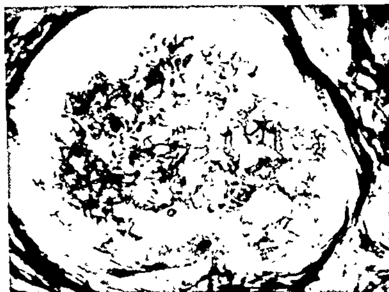


FIGURE 18 MICROSCOPIC SECTION OF NORMAL GLOMERULUS
Glomerulus from a normal kidney showing the delicate fibrils of reticulum Silver carbonate of Del Rio Hortega (After Fasciolo, 1939)

kidney since if the constricting clamp of the ischemic kidney was removed after six to nine months of ischemia in two thirds of the cases residual hypertension remained, the degree of which was related to the vascular lesions in the nonischemic kidney. Patton, Page and Ogden (1943) have made similar observations This residual hypertension was progressive since new lesions appeared even after removal of the ischemic kidney The objection has been raised that the lesions found in the nonischemic kidney may have existed before the production of ischemia of the other kidney. The experiments of Wilson

and Byrom (1941), however, suggest the possibility of a vicious circle—the hypertension produces vascular lesions which, by reducing renal blood flow, aggravate the pre-existing hypertensive state.

Chronic Eye Changes.—We have already discussed the acute ocular changes which occur in malignant hypertension. Keyes and Goldblatt (1937, 1938), Fasciolo and Cramer (1938), and Cramer (1940) studied other changes of a chronic nature in monkeys, dogs, and rats. The retinal vessels were observed ophthalmoscopically to be more tortuous

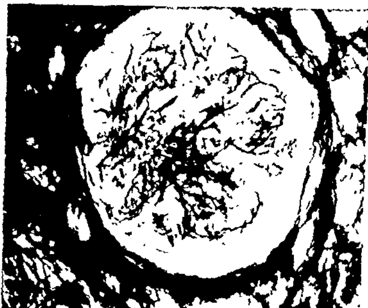


FIGURE 19 MICROSCOPIC SECTION OF ISCHEMIC GLOMERULUS

Glomerulus from an ischemic kidney Marked proliferation of fibrils of reticulum are observed Silver carbonate of Del Rio Hortega (After Fasciolo, 1939)

and the light reflex was increased, indicating early changes in the retinal vessels Hemorrhages, exudates, and separation of the retina appeared later. Microscopically, the arteriolar lesions consisted of hypertrophy and hyperplasia of the media, and later of hyalinization of the intima with tumefaction and proliferation of the endothelium (figure 20). The lumen of the vessel gradually became reduced and even occluded completely. The severity of the process varied considerably in different segments of the same vessel so that one part would appear perfectly normal and another completely obliterated

Laughlin, Thomas and Friedenwald (1910) studied the relationship between vascular changes observed ophthalmoscopically and those found histologically in hypertensive dogs. They were able to observe constrictions in arterial segments where there were no histologic abnormalities and concluded that such changes were due to vascular spasm.

Renal function is variable in hypertensive animals with chronic

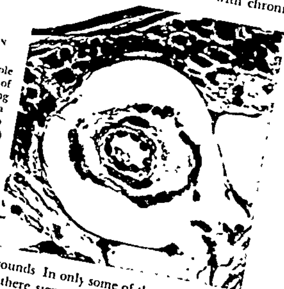


FIGURE 20. CHANGES IN RETINAL ARTERIES. Section of a small arteriole showing typical changes of arteriolar sclerosis consisting of medial hypertrophy, hyaline degeneration and endothelial hyperplasia. (×750) (After Laughlin, Thomas and Friedenwald, Bull. Johns Hopkins Hosp., 1910, 67, 79)

vascular lesions in the eyegrounds. In only some of the dogs of Keyes and Goldblatt (1938) were there signs of more or less pronounced renal insufficiency. The majority of Cramer's animals had a high specific gravity of the urine and no nitrogen retention. These data, however, do not exclude the possibility of renal excretory insufficiency. The retinal arterioles appear to be more sensitive than those in other parts of the body since they may develop degenerative changes while vessels in other parts of the vascular system are still normal.

CONVULSIVE UREMIA

We have already mentioned that convulsions may occur in dogs with marked constriction of one renal artery and contralateral nephrectomy and in those with constriction of both renal arteries. Until the introduction of Goldblatt's method, it was difficult to

reproduce experimentally the symptoms of convulsive uremia (Verney and Vogt, 1938). Symptoms and signs appear a variable length of time after producing ischemia and consist of hypertension and slight ataxia at the onset accompanied at times by muscular twitching Convulsions eventually appear characterized by rigidity of the trunk and extremities followed by clonic contractions. Separation of the retina may be observed at this stage. Although this syndrome is not always fatal, vomiting and intestinal hemorrhages appear if the disease progresses eventuating in death At autopsy petechial hemorrhages and exudations predominate.

The mechanism of production of experimental convulsive uremia is not entirely clear Its cause can not be attributed to nitrogen retention since the blood urea does not have to be particularly elevated. Bilateral nephrectomy, moreover, does not produce convulsive uremia. Verney and Vogt (1938) observed that complete ligation of the renal artery did not produce convulsions providing the function of the opposite kidney remained normal. Ligation of one renal artery with contralateral nephrectomy, on the other hand, readily produced the syndrome of convulsive uremia. The conditions necessary for the appearance of convulsive uremia appear to have a possible explanation in the investigations of Winternitz, Katzenstein, Mylon, Murphy and Zimmermann (1941) who observed that following ligation of both renal arteries in dogs, convulsions and hemorrhagic lesions of the meninges and brain occurred. These investigators also observed that convulsions and cerebral lesions could be reproduced in nephrectomized animals by the injection of extracts of such organs as kidney and testicle. It is possible, therefore, that the syndrome of convulsive uremia may be produced by cerebral lesions, edema, and hemorrhages, as a result of the formation of certain substances by renal autolysis.

Hypertension may be produced by partial constriction of the renal arteries in the absence of any alteration of excretory function of the kidney as measured by extremely sensitive functional tests (benign hypertension) If the renal ischemia is extreme, the hypertension is associated with a picture of severe renal insufficiency (malignant hypertension)

Both systolic and diastolic pressures become elevated without obvious change in pulse rate Pressure in the pulmonary artery re-

mains normal. No significant changes in blood volume, cardiac output, or blood chemistry occur. Vascular reflexes are little modified Intercurrent diseases and febrile reactions are apt to cause the blood pressure to fall

Pathologic changes found in benign hypertension of long duration are insignificant, consisting of some hypertrophy of the left ventricle and hypertrophy of the muscularis of the arterioles. In the kidney alone an increase of collateral circulation is occasionally encountered

In malignant hypertension, striking vascular changes characterized by hemorrhages and exudations occur. There is hyalinization of the intima microscopically with or without narrowing of the arterial lumen, and in more severe cases necrosis of the arterioles occurs Several factors are involved in the production of these vascular lesions such as the degree of renal insufficiency, the reabsorption of products of tissue autolysis, elevation of blood pressure, and probably vasoconstriction.

The retinal changes observed may be either acute or chronic. The acute lesions frequently appear in the course of the syndrome of convulsive uremia and are characterized by hemorrhages, exudates, and separation of the retina They may improve if the animal survives Chronic retinal lesions generally appear after several years of hypertension and are characterized by tortuosity of the retinal vessels, spasms, hemorrhages and exudates, according to the severity of the disorder.

CHAPTER III

MECHANISM OF PRODUCTION OF RENAL HYPERTENSION

In considering mechanisms involved in the production of hypertension, it should be remembered that various factors are concerned in the maintenance of blood pressure, such as blood volume, minute volume output of the heart, viscosity of the blood, and peripheral resistance.

As described in the previous chapter, the animal made hypertensive by constriction of the renal arteries has both systolic and diastolic hypertension without important changes of blood volume, cardiac output per minute, or blood viscosity. These findings indicate by exclusion that the hypertension can be attributed to an increase in peripheral resistance, i.e., to a diminution in the caliber of the arterioles. Granted this mechanism, the first possibility which presents itself as the cause of hypertension is that constriction of the renal arteries in itself produces sufficient obstruction to the passage of blood to produce hypertension by simple mechanical action. That this is not the case, however, is shown by the fact that unilateral or bilateral nephrectomy, i.e., complete removal of this vascular region, does not produce elevation of the blood pressure. Furthermore, constriction of arteries supplying other tissues, such as the femorals, splanchnics, mesenterics, celiacs, and so forth, does not produce hypertension despite the extensive vascular area concerned. It is therefore evident that local mechanical obstruction can not be held responsible for the hypertension and that the explanation must be sought in a generalized change of the vascular system.

The increase of peripheral resistance can be organic or functional. That the reduction of vascular caliber is predominantly functional is indicated by the following findings: (a) It is possible to obtain hypertension by renal ischemia without histologic changes of the vessels (benign hypertension), (b) Removal of the ischemic kidney, even after long periods of hypertension, causes the blood pressure to become normal within a few hours; (c) Arteriolar constriction

in the eyegrounds (Laughlin, Thomas and Friedenwald, 1940) and in the ear vessels of hypertensive rabbits (Abell and Page, 1942b) have been observed directly.

The existence of a generalized vasoconstriction in animals with renal ischemia might be due to a nervous reflex mechanism of renal origin or else to a humoral mechanism produced by the presence of vasoconstrictor substances in the blood. In this chapter, investigations which have been carried out to elucidate these points will be discussed.

NERVOUS MECHANISM

EFFECT OF RENAL DENERVATION. If renal ischemia or other change produces a pressor reflex of renal origin, section of the afferent pathways of the reflex arc (renal nerves), of the central nerves (medulla), or of the efferent pathways (sympathetic nervous system) should prevent the appearance of the hypertension or else cure a pre-existing one.

Renal denervation has been repeatedly investigated in hypertension from renal ischemia (Page, 1935a, Collins, 1936, Vallery-Radot, Blondin, Israel and Cachin, 1938) Denervation of the renal pedicle in dogs does not modify the blood pressure and does not prevent the development of hypertension by subsequent constriction of the renal artery (see figure 21) Although all precautions possible for the total destruction of the nerves of the renal pedicle were taken in these experiments (painting with phenol, histological evidence, and so forth) it is possible that some fibers remained intact or that the kidney maintained some nervous connection through its capsule In order to overcome these objections, Glenn, Child and Heuer (1937) transplanted a kidney by anastomosing it to the femoral vessels Blalock and Levy (1937) obtained similar results by transplanting kidneys into the neck. After several days, constriction of the artery produced a definite rise of blood pressure Acute experiments, lasting only a few hours in anesthetized animals, also showed that a rise of blood pressure was obtainable from ischemia of completely isolated kidneys, circulation to which was maintained by vascular anastomosis (Houssay and Fasciolo, 1937b, Enger and Gerstner, 1938, Braun-Menéndez and Fasciolo, 1939a, b). These results were conclusive in demonstrating the impossibility of preventing hypertension from renal ischemia by renal denervation

Results with other types of renal hypertension are less conclusive. According to Dicker (1937e) and Enger and Gerstner (1938), denervation of the kidney did not prevent the rise of pressure produced by ligation of the ureters. Braun-Menéndez (1932) found that after renal denervation, constriction of the renal vein did not produce hypertension. Arnott and Kellar (1936) observed that denervation

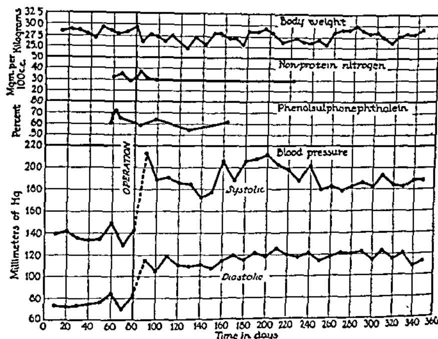


FIGURE 21 EFFECT OF DENERVATION OF THE KIDNEYS AND CONSTRICTION OF THE RENAL ARTERIES

In the case of the blood pressure, each point represents an average of the readings taken over a period of ten days. Note that renal denervation does not prevent the production of hypertension (After Collins, Am. J. Physiol, 1936, *116*, 616)

of the kidney prevented the hypertension produced by sodium oxalate in rabbits. Maegraith and McLean (1938) found that the injection of a suspension of kieselguhr into the renal artery of rabbits produced a transitory hypertension in the animals that survived. Denervation of the kidney rapidly caused the pressure to become normal in these animals. The effect of renal denervation on other types of hypertension (neurogenic and central) has been discussed in Chapter I. The contradictory results obtained in hypertension,

produced by procedures other than that of compression of the renal arteries, are difficult to interpret. It is possible but not probable that the mechanism of production of the hypertension is different. Renal denervation may produce a greater renal blood flow or the operation performed may facilitate the formation of a collateral circulation in some way. Occasional variations may be attributed to the difficulty of predicting the production of hypertension and to the transitory nature of experimental hypertension.

Observations on renal denervation indicate that hypertension from renal ischemia is not due to a pressor reflex originating in the kidney It is possible, however, that the function of the central nervous system in the spinal cord or bulbar region is altered by humoral mechanisms, in which case section of the efferent pathways or of the central nerves should cause the elevated blood pressure to return to normal.

OPERATIONS ON THE SYMPATHETIC NERVOUS SYSTEM

Goldblatt, Gross and Hanzal (1937) excised the splanchnic nerves in the thoracic region and removed the last four thoracic ganglia In these animals partial constriction of the renal arteries produced the usual hypertension In dogs with pre-existing hypertension of as long as four years' duration, section of the splanchnics did not produce a permanent fall of blood pressure. Blalock and Levy (1937) were unable to prevent the rise of blood pressure in dogs by subdiaphragmatic section of the splanchnics, resection of the celiac ganglion and of the superior lumbar ganglion associated with bilateral partial adrenalectomy (operation of Adson and Craig) Introzzi, Canónico and Taiana (1938) found that resection of the splanchnic and lumbar sympathetics neither prevented nor cured hypertension produced by renal ischemia Combining these nervous resections with partial removal of both adrenals, a fall of blood pressure was obtained in three of four hypertensive dogs

Resection of the anterior cord roots between the sixth thoracic and second lumbar inclusive, which carry sympathetic fibers, neither prevented nor lowered the hypertension produced by constriction of the renal arteries of the dog (Goldblatt and Wartman, 1937)

Complete resection of the paravertebral ganglia from the stellate ganglion to the pelvic chain did not significantly prevent, cure, or modify hypertension produced by constriction of the renal arteries

in dogs (see figure 22) (Heymans, Bouckaert, Elaut, Bayless and Samaan, 1937, Alpert, Alving and Grimson, 1937; Freeman and Page, 1937). These wide ablations of sympathetic nerves, however, leave the paravertebral ganglia intact This occurs even though their con-

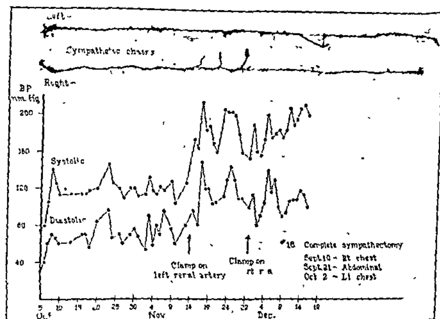


FIGURE 22 EFFECT OF SYMPATHECTOMY ON DEVELOPMENT OF RENAL HYPERTENSION

Effect of constriction of the renal arteries on the systolic and diastolic pressure of a dog in which both paravertebral sympathetic chains were removed from the stellate ganglion to the pelvic chain The unbroken sympathetic chains removed are shown in the upper part of the chart. Note that sympathectomy does not prevent the production of hypertension (After Freeman and Page, Am Heart J, 1937, *14*, 405)

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DESTRUCTION OF SPINAL CORD Glenn, Child and Page (1938) found that destruction of the spinal cord below the fifth cervical nerve produced a dramatic fall of pressure in dogs with

hypertension from renal ischemia. The pressure rose after several days reaching higher levels than those observed before the ischemia, but did not reach the hypertensive level present before destruction of the cord Destruction of the cord previously did not prevent hypertension from renal ischemia (Glenn and Lasher, 1938a)

These results are difficult to reconcile with those obtained by Dock and his collaborators[1] and House and Wakerlin (1941a, b) who found that acute destruction of the nervous system in normal and hypertensive rats, rabbits and dogs lowered the pressure to the same level regardless of the initial blood pressure. From their observations, they concluded that in renal hypertension there are no circulating vasoconstrictor substances with a peripheral action, but rather that the vasomotor center is maintaining the pressure at a higher level than normal It is difficult to accept such conclusions which are based on experiments which are so traumatic that they produce a state of shock with a fall of blood pressure to only a few millimeters of mercury Their opinion that the renal pressor hormone acts through the vasomotor nervous control mechanism is not reconcilable with the fact that procedures which sever the vasomotor center from its efferent nervous connections, such as sympathectomy, are incapable of permanently curing, preventing or modifying the hypertension produced by renal ischemia The effect of sympathectomy on hypertension of extrarenal origin has been discussed in Chapter I

In connection with sympathectomy, it should be mentioned that extirpation of the adrenal medulla in dogs does not prevent hypertension from renal ischemia (Goldblatt, Lynch, Hanzal and Summerville, 1931, Fasciolo, 1938b)

HUMORAL MECHANISM

The evidence just discussed indicates that hypertension from renal ischemia can not be explained on the basis of a nervous mechanism. The arteriolar vasoconstriction must be due, therefore, to the presence of vasoconstrictor substances in the blood At this point in our discussion, this conclusion must be considered to be entirely hypothetical since it is based on indirect evidence Unless conclusive proofs of the existence of a hypertensive substance causing renal

[1] Dock and Rytand, 1934, Dock, 1940a, b, Dock, Shidler and Moy, 1942

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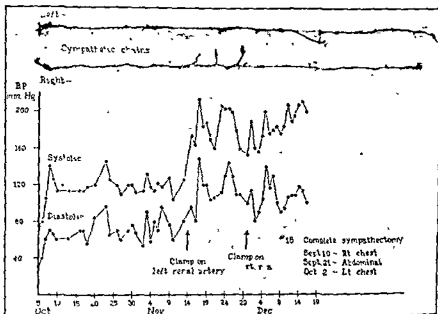


Figure 22 Effect of Sympathectomy on Development of Renal Hypertension

pressure om the stellate ganglion to the pelvic chain ... emoved ... part of the chart Note that sympathectomy does not ... Am Heart J.

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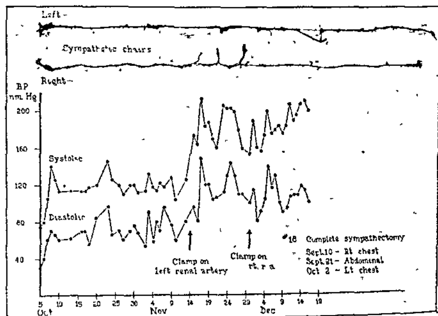


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PRESSOR SUBSTANCES IN RENAL VENOUS BLOOD. Proof that the ischemic kidney liberates pressor and vasoconstrictor substances into the blood was offered by Houssay and Fasciolo (1937a, b) by demonstrating a pressor effect from grafting ischemic kidneys into the necks of nephrectomized dogs, and by Houssay and Taquini (1938a) by demonstrating vasoconstrictor activity in the renal venous blood of ischemic kidneys

Kidneys were grafted into dogs anesthetized with chloralose and bilaterally nephrectomized two hours previously The bilateral nephrectomy was carried out with the idea of making the animals more sensitive to the action of the pressor substance (see Chapter IX) The graft consisted of uniting the renal artery with the carotid and the renal vein with the jugular (see figure 23) Details of the technique are described in the appendix

Kidney grafts from 24 dogs with renal hypertension of 2 to 40 days' duration produced an elevation of the recipient's blood pressure in 22 cases (figure 24) The pressure began to rise a few minutes after establishing the circulation and gradually reached a maximum at the end of about five minutes. The pressure usually remained elevated for as long as two or three hours after the removal of the grafted kidney (see figure 26) Rises obtained varied between 20 and 60 mm. Hg and bore no obvious relation to the pressure of the donor dog Many of the kidney grafts produced both systolic and diastolic hypertension in the recipient without changing the pulse rate In some cases, the mean pressure rose above 200 mg Hg The kidneys, when grafted into a second recipient, also produced a rise

hypertension are obtained, it is only justifiable to refer to it as the "hypothetical pressor substance."

Such a hypothetical pressor substance might arise from retention of substances normally eliminated by the kidney and endowed, as in the case of guanidine, for example, with a pressor action. Such a mechanism appears to be improbable since bilateral nephrectomy does not cause the blood pressure to rise, while unilateral ischemia produces hypertension without producing the slightest excretory insufficiency of the kidney. These facts, as well as the observation that extirpation of the ischemic kidney causes blood pressure to return rapidly to normal, makes one think that the ischemic kidney produces and liberates into the blood stream one or several vasoconstrictor substances which cause the pressure to rise. The validity of such an interpretation has been demonstrated in the experiments which are to be described.

Pressor substances have been investigated in the kidney, renal venous blood, systemic blood, and other body fluids. We will refer only to the experiments performed on animals with hypertension Experiments concerned with acute renal ischemia, perfusion of the kidney, and renin will be described in Chapter VIII.

PRESSOR SUBSTANCES IN RENAL TISSUE. The first attempts to investigate the presence of pressor substances in ischemic kidneys were carried out by Harrison, Blalock and Mason (1936) and by Prinzmetal and Friedman (1936) who observed that extracts of kidneys in Ringer's solution, injected intravenously to unanesthetized dogs produced an initial hypotension which was more or less marked, followed by a definite rise of blood pressure to a higher level than that initially present. Extracts of ischemic kidneys of hypertensive dogs had less depressor and more pressor action than extracts of normal kidneys. The kidneys of patients with hypertension appeared to have a greater pressor action than did the kidneys of patients with normal blood pressure. These experiments were suggestive but not conclusive since a sudden fall of blood pressure can be followed by a pronounced rise even in the absence of any pressor substance. The results described, however, represented an average of many trials, and in that sense may have been significant.

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of blood pressure (see figure 26) indicating that the results obtained were attributable to a pressor secretion of the kidney rather than to a transfer of substances which had accumulated during the operative procedure. Control experiments were carried out by grafting 25 kidneys from normal dogs In 21 cases there was no change in

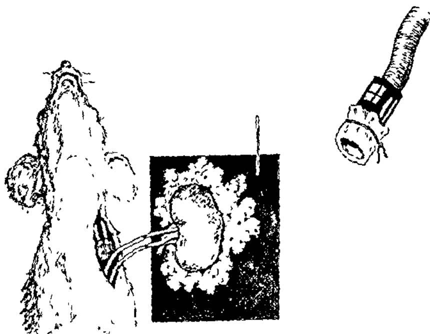


FIGURE 23 KIDNEY GRAFTED INTO THE NECK OF A DOG BY ARTERIAL AND VENOUS ANASTOMOSES

The kidney is shown lying on a heated plate with a thermometer. At the right, a vessel with a Payr's cannula (After Fasciolo, 1939)

the recipient's blood pressure, and in 4 the blood pressure rose (figure 25)

The results of one experiment are reproduced in figure 27 which illustrates the result of grafting a kidney with two arteries, only one of which was constricted previously. Establishment of the circulation through the ischemic tissue produced a rise of blood pressure while that through the normal portion produced no change.

Dicker (1937f) grafted ischemic kidneys into three nephrectomized dogs In three days he observed a slight rise of blood pressure.

Bouckaert, Grimson and Heymans (1939), confirming the results

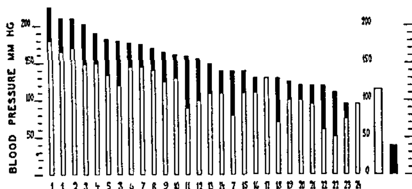


FIGURE 24 KIDNEY GRAFTS FROM HYPERTENSIVE DOGS INTO THE NECK OF NEPHRECTOMIZED DOGS

Results of 24 grafts White columns initial blood pressure. Black columns rise of pressure after the graft Wide columns at right average figures Figures at the foot of each column indicate the number of the experiment Those with identical numbers correspond to different animals in which the same kidney was grafted Note that a definite rise of blood pressure occurred in all but two experiments (After Fasciolo, 1939)

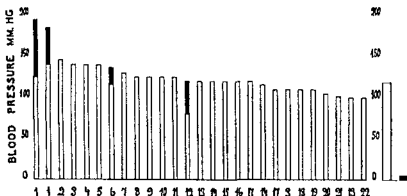


FIGURE 25. KIDNEY GRAFTS FROM NORMAL DOGS INTO THE NECK OF NEPHRECTOMIZED DOGS

See legend for figure 24 Note that no rise of blood pressure occurred in all but four experiments (After Fasciolo, 1939).

of Houssay and Fasciolo, observed a rise of blood pressure in seven of nine grafts of ischemic kidneys performed under satisfactory conditions. The results obtained by Govaerts (1939) were less conclusive. In a total of ten grafts of ischemic kidneys, a pressor effect was obtained in only six cases. Govaerts and Muller (1939a, b) studied the effect of normal kidney grafts on the blood pressure of nephrectomized dogs. If the graft was made in animals nephrectomized two hours previously, the pressor action was slight or none at all

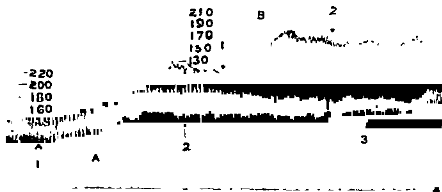


FIGURE 26 PRESSOR ACTION FROM THE GRAFT OF AN ISCHEMIC KIDNEY

Blood pressure of two chloralosed, recently nephrectomized dogs in which an ischemic kidney from a hypertensive dog was grafted. A) At 1, the kidney from a hyp-
graf
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Hou

In dogs nephrectomized two days before, a considerable rise was obtained. By means of cross-circulation experiments, they came to the conclusion that the difference was due to an increased sensitivity of the animal nephrectomized 48 hours previously to the pressor substance secreted by the kidney.

It may be concluded from the above observations that the ischemic kidney is capable of secreting a pressor substance and liberating it into the general circulation. The cause of some of the negative results is not entirely clear. The sensitivity of the animal receptor may have been a factor of importance. The negative results obtained by

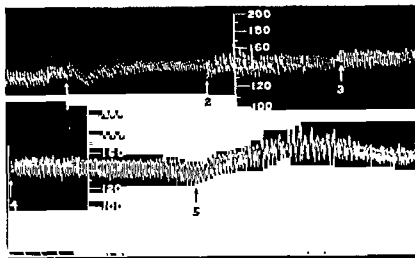


FIGURE 27 GRAFT OF NORMAL AND ISCHEMIC REGIONS OF A KIDNEY WITH TWO RENAL ARTERIES

Blood pressure in mm. Hg of a chloralosed dog bilaterally nephrectomized previously At 1, a kidney from a normotensive was grafted. At 2, the graft was removed At 3, the unconstricted artery of the ischemic kidney was anastomosed.

Boylston, McEwen and Ivy (1938) were probably due to technical difficulties.

VASOCONSTRICTOR SUBSTANCES IN RENAL VENOUS BLOOD. The experiments of Houssay and Taquini (1938a) showed that the blood coming from ischemic kidneys *in situ* possessed vasoconstrictor properties. Using a wide abdominal incision, blood was taken from the renal vein under general anesthesia, special precautions being taken in all cases to avoid contamination with blood coming from the adrenal. The donor dogs usually had hypertension of only a few days' duration. Blood pressure in all cases exceeded *180 mm Hg. About 50 cc. of blood were withdrawn from the renal* vein and diluted with an equal volume of calcium-free Ringer's solution It was then centrifuged and the plasma mixed with Ringer's

solution to a final dilution of 1.8. The blood was kept from coagulating since clotting is accompanied by the formation of vasoconstrictor substances (see Chapter XI). Renal venous blood was taken from normal animals by a similar technique. The vasoconstrictor action was tested on the isolated vascular system of the toad using the technique of Lawen-Trendelenburg which consists of perfusing

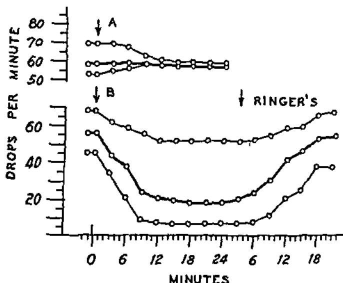


FIGURE 28 VASOCONSTRICTOR ACTION OF RENAL VENOUS BLOOD ON THE VASCULAR SYSTEM OF THE TOAD, *Bufo Arenarum* HENSEL ACCORDING TO THE LÄWEN-TRENDELENBURG METHOD

A Venous blood plasma from normal kidneys, B Plasma from venous blood of [illegible] greatest and [illegible] repre- [illegible] te the [illegible] oussay [illegible]

the substances to be examined through the vessels of the hind limb of the eviscerated toad. Variations in the number of drops which flow from the abdominal vein indicate constriction or dilatation of the vessel Details of the technique have been discussed by Houssay and Taquini (1938a, b)

Plasma of the blood coming from ischemic kidneys of 15 hypertensive dogs produced in all cases a diminution in the number of

drops varying between 23 and 85 per cent Plasma coming from the kidneys of 15 normal dogs produced a minimal reduction in ten cases and a slight increase in five The most marked diminution in the number of drops obtained with plasma of normal kidneys was 14 per cent The 15 hypertensive animals gave an average reduction in the number of drops of 63 per cent, while the 15 normal animals gave an average reduction of only 3 per cent (see figures 28 and 29)

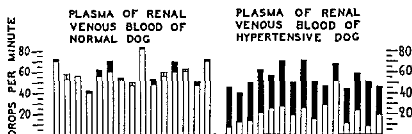


FIGURE 29 VASOCONSTRICTOR ACTION OF RENAL VENOUS BLOOD OF NORMAL AND HYPERTENSIVE DOGS

Vasoconstrictor action of citrated blood plasma in a vascular preparation of the toad *Bufo arenarum* Hensel according to the Lawen-Trendelenburg method Perfusion with citrated plasma of venous blood of normal kidneys (left), and citrated plasma of venous blood of ischemic kidneys (right) of hypertensive dogs Each column corresponds to one plasma, the height indicates the initial number of efferent drops from the preparation perfused with Ringer's solution The decrease in drops is indicated by the black columns, the increase by the striped columns Note the constrictor action of the renal venous blood from hypertensive dogs (After Houssay and Taquini, Rev Soc argent de biol, 1938, *14* 5)

The systemic blood and the venous blood of other organs of hypertensive dogs always had a vasoconstrictor action which was less than that coming from the renal vein, and in many cases no effect could be demonstrated (Houssay and Taquini, 1938b) (see figure 30)

These results have recently been confirmed by Goldblatt, Kahn and Lewis (1941) The negative results published by Mason and Rozzell (1939), and by Wakerlin and Salk (1941) were probably due to the use of a different species or to slight differences in technique Houssay, Fasciolo and Taquini (1938) also showed that the renal venous blood of hypertensive dogs possessed a vasoconstrictor action on the denervated dog leg

The existence of pressor and vasoconstrictor substances in the

renal venous blood of hypertensive dogs appears to be conclusive and further evidence is given in Chapter VIII. The majority of the experiments which we have mentioned (renal grafts, vasoconstrictor substances in the renal venous blood) were performed on animals with hypertension of short duration and with an associated renal insufficiency. It is to be questioned if the same results would be

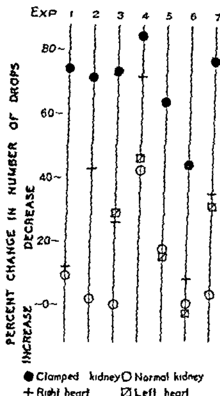


FIGURE 30: VASOCONSTRICTOR ACTION OF THE BLOOD OF HYPERTENSIVE DOGS

The vasoconstrictor effect of the plasma of blood from different organs of 7 dogs made hypertensive by unilateral renal ischemia was demonstrated on the Läwen-Trendelenburg preparation. It is to be noted that the blood which had the greatest constrictor action came from the renal vein on the ischemic side. Blood from the non-ischemic kidney always had less constrictor action (After Houssay and Taquini, Rev. Soc. argent. de biol., 1938, *14*, 86).

obtained in chronically hypertensive animals without renal insufficiency.

PRESSOR SUBSTANCES IN THE SYSTEMIC BLOOD Search for pressor substances in the systemic blood of hypertensive animals has been fraught with difficulty. Prinzmetal, Friedman and Rosenthal (1936) were unable to demonstrate vasoconstrictor action by perfusion of the systemic blood of hypertensive dogs through the tail. Negative results were likewise obtained with a different technique by Heymans and Bouckaert (1938) and by Wakerlin and Yanowitz

(1939a, b). Page (1936a) and Prinzmetal, Friedman and Oppenheimer (1938) found no difference in the pressor action of extracts of blood of normal and hypertensive dogs. Euler and Sjöstrand (1943) reported a reduction in the amount of a pressor substance insoluble in ethyl alcohol and soluble in methyl alcohol in the plasma of patients with essential hypertension and chronic nephritis as compared with normal controls.

Collins and Hoffbauer (1937) transfused a normal dog with blood from a hypertensive dog in an amount equivalent to 20 per cent of its body weight without producing an elevation of blood pressure. Negative results have also been reported by Katz, Friedman, Rodbard and Weinstein (1939) who, by means of cross-transfusions between hypertensive dogs and unanesthetized nephrectomized recipients, exchanged 700 to 2,400 cc of blood in the course of ten or more hours. By perfusing the leg with arterial blood from hypertensives, no significant vasoconstrictor activity was demonstrable. A few similar experiments performed by Houssay and Fasciolo (unpublished) also gave negative results

Solandt, Nassim and Cowan (1940), using an appropriate cross-circulation technique, transferred approximately three liters of blood per hour from hypertensive to nephrectomized dogs In seven successful experiments, they obtained rises of blood pressure in the nephrectomized animal. The duration of the pressure rise was variable and its magnitude varied between 20 and 50 mm. Hg In non-nephrectomized recipients, no rise of pressure could be obtained. Transfusions between 20 normal dogs and between four normal and nephrectomized dogs produced no elevation of blood pressure Some of the results obtained by these authors may not have been due to the presence of specific pressor substances preformed in the systemic blood of the hypertensive dog It is known that transfusions frequently produce a fall of pressure in the recipient as a result of incompatability of blood Following these abrupt falls of pressure, there may be a rise above the initial level. In some of the recipients of Solandt, Nassim and Cowan, the rises were small and hardly sufficient to exclude spontaneous variations The marked fall of pressure which was observed in some of the hypertensive dogs might have produced a liberation of renin, which could then have been the agent responsible for the rise of pressure in the nephrectomized recipients

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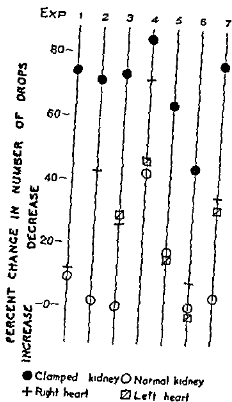


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Freeman (1940) reported that the transfusion of 200 cc. of normal dog blood to hypertensive dogs resulted in a fall of blood pressure which did not occur when hypertensive blood was injected into normal or into hypertensive recipients. According to these results, the blood of hypertensives would be lacking in a depressor principle

MECHANISM OF ACTION OF THE PRESSOR SUBSTANCE OF ISCHEMIC KIDNEYS

The results which have just been discussed indicate that in the renal venous blood of hypertensive animals there are one or more

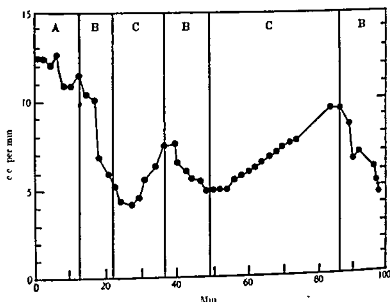


FIGURE 31 VASOCONSTRICTOR ACTION OF VENOUS BLOOD FROM AN ISCHEMIC KIDNEY

Perfusion of the denervated leg of a dog with defibrinated blood (A) Blood from the heart-lung circuit after functioning one hour, (B) venous blood from ischemic kidney, (C) venous blood from kidney with normal flow Note the marked vasoconstrictor action of the blood from the ischemic kidney (After Braun-Menéndez, Fasciolo, Leloir and Muñoz, J. Physiol, 1940, 98, 283)

substances with a pressor and vasoconstrictor action The next logical step was to study the chemical and pharmacologic properties of this pressor substance for the purpose of its isolation This necessitated the use of large quantities of renal venous blood of hypertensive animals The preparation of hypertensive animals, however, was

laborious and difficult. In some cases the yield of pressor principle was small. If it had been necessary to use the hypertensive dog as a source of pressor material, progress would have undoubtedly been slow and difficult The investigations of Enger, Linder and Sarre (1938a), Verney and Vogt (1938) and Grimson (1939) had shown that hypertension develops within a few minutes of inducing renal ischemia These studies were repeated in some detail by Braun-Menéndez and Fasciolo (1939a) who showed that a diminution of 80 to 90 per cent of renal blood flow produced pressor and vasoconstrictor activity in the renal venous blood within a few minutes

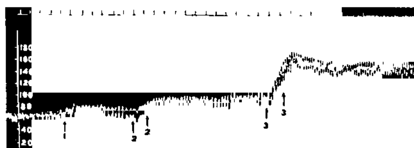


FIGURE 32 PRESSOR ACTION OF VENOUS BLOOD FROM AN ACUTELY ISCHEMIC KIDNEY

Injection of venous blood coming from a kidney incompletely ischemic for one hour Dog of 17 kgm chloralosed and nephrectomized Femoral blood pressure in mm Hg At (1), injection of 100 cc of normal saline into the jugular vein, at (2) beginning and end of injection of 100 cc of jugular blood, at (3), beginning and end of injection of 100 cc of renal venous blood. Time in minutes Note the pressor action of the venous blood from the ischemic kidney (After Braun Menéndez and Fasciolo, Rev Soc. argent de biol, 1939, *15*, 161).

(figure 31) Kidneys were perfused either by means of the heart-lung preparation or by grafting them into the neck of another dog After a brief period of ischemia, 20 to 40 cc of renal venous blood had a strong pressor action in dogs when injected intravenously (see figures 32 and 33).

By means of this technique, Braun-Menéndez and Fasciolo (1939b) carried out a pharmacologic study of the pressor substance and showed that its action persisted after bilateral vagotomy, atropinization (1 mgm per kgm), cocainization (10 mgm per kgm), or injection of Fourneau 933 (10 mgm per kgm of body weight) (see figure 34).

Nephrectomized animals were shown to have an increased sensitivity to the pressor substance.

Braun-Menéndez, Fasciolo, Leloir and Muñoz (1939) extracted this pressor substance from the venous plasma of kidneys with acute incomplete ischemia by the addition of three volumes of acetone. They called it *hypertensin*. When injected intravenously, it produced a rise of blood pressure in the dog. It was thermostable and insoluble in

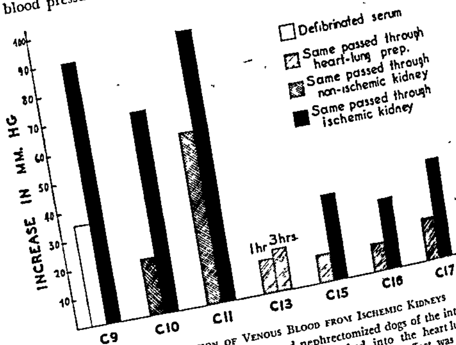


FIGURE 33 PRESSOR ACTION OF VENOUS BLOOD FROM ISCHEMIC KIDNEYS Effect on blood pressure of chloralosed and nephrectomized dogs of the intravenous injection of venous blood from kidneys grafted into the heart lung preparation Note that in each experiment the greatest pressor effect was obtained from venous blood from the acutely ischemic kidney (After Braun-Menéndez and Fasciolo, Rev Soc argent de biol, 1939, *15*, 161).

ether Its pressor effect lasted only three to four minutes It possessed a vasoconstrictor action on the vascular system of the toad. Its chemical and pharmacologic properties were different from those of oth pressor substances known at that time.

Hypertensin was quite different from renin, the pressor substa discovered by Tigerstedt and Bergman (1898) in the renal cort Renin was thermolabile, did not dialyze, and its pressor action

prolonged (20 minutes or more), while hypertensin was thermostable and dialyzable, and had a short pressor action. Ischemic kidney grafts as well as the injection of blood coming from acutely ischemic kidneys produced a prolonged pressor effect which was more easily attributable to renin than to hypertensin If renin was the substance

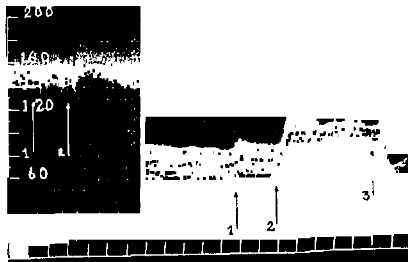


FIGURE 34 ACTION OF FOURNEAU 933 ON THE PRESSOR ACTION OF VENOUS BLOOD FROM AN ACUTELY ISCHEMIC KIDNEY

Twelve kgm. dog anesthetized with chloralose Femoral blood pressure in mm. Hg. Time [illegible]
vein; (2) [illegible]
gamma [illegible]
kgm of [illegible]
pressor action of venous blood from the ischemic kidney (After Braun-Menéndez and Fasciolo, Rev Soc argent. de biol, 1939, *15*, 401)

causing the rise of blood pressure in these cases, it was difficult to explain the significance of the hypertensin which had been demonstrated in the renal venous blood.

In order to clarify this point, attempts were made to produce hypertensin *in vitro* by incubating renal cortex with blood serum under conditions of anoxia The results were negative in that there was no evidence of the formation of any pressor substance. When,

however, an extract containing renin instead of crude renal cortex was incubated at 37°C. for ten minutes with blood serum, a pressor substance was formed which was identical with the hypertensin extracted from the renal vein (Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1939) (figure 35).

Several points suggested that renin behaved as an enzyme and that

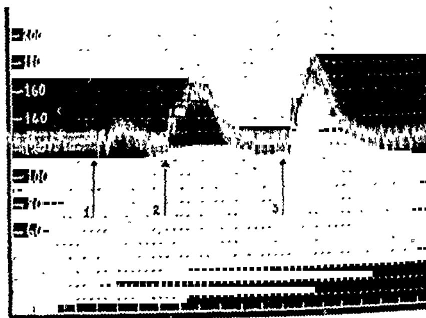


FIGURE 35 FORMATION OF HYPERTENSIN "IN VITRO"

Eight kgm vagotomized dog anesthetized with chloralose. Artificial respiration Blood pressure in mm. Hg Time in minutes Intravenous injection of extract of (1) 70 cc of serum and 3.3 cc of renin incubated separately, (2) 70 cc of serum and 3 3 cc of renin incubated for five minutes at 37°C; (3) 70 cc. of serum and 3 3 cc of renin incubated for 30 minutes at 37°C. (After Braun Menéndez, Fasciolo, Leloir and Muñoz, Rev Soc argent de biol, 1939, *15*, 420)

it acted on a substrate present in plasma to give rise to the formation of hypertensin. The name precursor of hypertensin, or *hypertensinogen*, was given to the plasma substrate.

Similar results were obtained simultaneously in the United States by Page and Helmer, although they pursued an entirely different approach to the problem. Kohlstaedt, Helmer and Page (1938) found that purified renin produced a rise of blood pressure when injected

intravenously into intact animals but did not produce vasoconstriction if it was dissolved in Ringer's solution and perfused through the vessels of the dog's tail or the rabbit's ear. Kohlstaedt, Page and Helmer (1940) showed that its vasoconstrictor activity could be re-established by the addition of plasma proteins To this plasma protein, they gave the name renin-activator, indicating that renin was inactive as the pressor substance without its activator The combination of two substances without vasoconstrictor activity, i e, purified renin and its activator, therefore gave rise to a third with a constrictor action Page and Helmer (1940a, c) called this constrictor substance angiotonin

Hypertensin and angiotonin are the same substance and hypertensinogen and renin-activator are synonyms These substances will be discussed in greater detail in their respective chapters

From the foregoing, it may be concluded that renin is not in itself a pressor substance but that its pressor activity depends on its ability to form hypertensin in the organism These conclusions are supported by the following observations (a) Purified renin possesses no vasoconstrictor activity, (b) all the pharmacologic effects of renin can be explained by the formation of hypertensin, (c) when hypertensinogen is removed from the blood by injections of renin, the renin, itself, also loses its pressor activity The most definite evidence, however, has come from studies of its specificity Fasciolo, Leloir, Muñoz and Braun-Menéndez (1940a) observed that pig renin did not produce hypertensin when incubated with human plasma Incubation of the same plasma with human renin, however, gave rise to the formation of hypertensin On the basis of these *in vitro* experiments, they predicted that pig renin would not have a pressor action in man, a prediction which was confirmed by the results of Battro, Braun-Menéndez, Lanari and Leloir (1940)

Although incubation of renin with serum or plasma gave rise to the formation of hypertensin, prolongation of incubation destroyed the hypertensin It was shown that this destruction of hypertensin was due to an enzyme present in the kidney which was called *hypertensinase* Hypertensinase is found throughout the body, including the *blood*

It remained to be seen if, as a result of ischemia, the kidney secreted hypertensin, or if it secreted renin which in turn gave rise to

hypertensin in the blood through the *action of renin on hypertensinogen.*

Leloir, Muñoz, Braun-Menéndez and Fasciolo (1940a) *showed that* the ischemic kidney secreted renin rather than hypertensin, since the venous blood of the ischemic kidney contained *no hypertensin,* but hypertensin appeared rapidly when the blood remained at room temperature or at 37°C. for a few minutes. Similar results have been obtained by Kohlstaedt and Page (1940b).

In summary we may say that renin is secreted by the ischemic kidney and transforms a small part of hypertensinogen into hypertensin, which is the substance responsible for the rise of blood pressure. Hypertensin is rapidly destroyed by hypertensinase. The rise of pressure obtained from an injection of renin is prolonged since the production of hypertensin continues as long as renin circulates A single injection of hypertensin, however, produces a rise of pressure of only three to four minutes' duration, probably because it is rapidly destroyed by hypertensinase With a continuous infusion of hypertensin, the blood pressure remains elevated for longer periods In the chapters which follow, renin, hypertensinogen, hypertensin, and hypertensinase will be discussed in detail.

Studies of animals hypertensive from renal ischemia indicate that the hypertension is due to a generalized vasoconstriction.

This type of hypertension can be neither prevented nor cured by renal denervation, total paravertebral gangliar sympathectomy, *resection of the anterior cord roots, or destruction of* the spinal cord. This shows that the generalized vasoconstriction is of humoral rather than of nervous origin. The substance causing the hypertension is not a metabolic product retained as a result of renal insufficiency.

A pressor and vasoconstrictor substance is present in the renal venous blood of animals made hypertensive by partial constriction of the renal artery. The renal venous blood of acutely ischemic kidneys also possesses pressor and vasoconstrictor activity. The substance responsible for this action is renin. Renin is a protein and has no vascular action of its own. Its pressor and vasoconstrictor *activity* depend upon hypertensin, which is a substance formed by the interaction of renin with hypertensinogen, *the* [illegible] *ing a globulin* present in blood plasma. T[illegible], destroyed by hypertensinase.

CHAPTER IV

RENIN

In 1898, Tigerstedt and Bergman observed that saline extracts of kidney produced a rise of blood pressure when injected intravenously. They partially purified the active substance and called it "renin." This name, now well established by use, has the inconvenience of being confused with the gastric enzyme, rennin, which has the property of coagulating milk. Fortunately, the name of the gastric enzyme is little used.

GENERAL PROPERTIES

From its properties, renin may be considered to be a protein although it has not been obtained in pure state.

STABILITY. As a dry powder it remains stable for more than a year. When purified it may be dried from the frozen state without losing activity. It remains active as a solution for many months in the icebox when toluol or other preservative is added. According to Katz and Goldblatt (1943), extremely purified renins lose activity when dissolved in distilled water. Their stability is greater if dissolved in 1 per cent sodium chloride. According to Pickering and Prinzmetal (1938a), it remains unaltered at pH 4 for two months in the icebox, but at pH 10 all activity disappears within two weeks.

Pig renin is stable at 37°C at pH 3.7 to 3.9 for a period of 30 minutes. It begins to be destroyed at a lower pH (Leloir, Muñoz, Braun-Menéndez, and Fasciolo, 1940b). Human renin appears to be destroyed more easily by acid, although precise data are not available.

Heating to 50 to 55°C for 15 minutes does not destroy the activity, but above a temperature of 56°C it is rapidly destroyed (Helmer and Page, 1939).

PRECIPITABILITY. Renin is precipitated from aqueous solutions by adding ammonium sulphate to a concentration of 1.4 to 2.6 molar

at pH 6 (Katz and Goldblatt, 1943). It is also precipitated with 0.38 to 0.41 saturated ammonium sulfate at pH 5, with saturated sodium chloride at pH 2 to 3, and with 0 7 to 1.0 saturation with magnesium sulfate (Collings, Remington, Hays and Drill, 1940) It is not precipitated by acidification at any pH, at least in dilute solutions

Alcohol and acetone (2 to 3 volumes) precipitate renin from aqueous solution. Unless the temperature is kept low, however, losses may be considerable The destructive action of these solvents is not so great on minced kidney

REACTIONS The renin purified by Collings and collaborators (1940) gave the following positive reactions: biuret (peptide linkage), Millon (tyrosine, phenols), xanthoproteic (benzene ring), Hopkins-Cole (tryptophane), Ehrlich-diazo (histidine, tyrosine), and Sakaguchi (arginine). Negative reactions were obtained with Molisch (carbohydrate), Sullivan (cystine, cysteine) and benzidine (pentose) Reactions for sulfhydryl groups were negative even after denaturation and treatment with cyanide By fusion with sodium, however, the presence of sulfur could be detected in the preparation. The renin purified by Plentl and Page (1944b) was shown to contain carboxypeptidases, pepsinases, trypsinases, and aminopeptidases.

ADSORBENTS Laufberger (1937) purified renin by chromatographic adsorption using a column of calcium carbonate According to Hessel (1938a, b), and McEwen, Harrison and Ivy (1939), renin was adsorbed on kaolin (10 per cent) at pH 3 5 and was eluted with disodium phosphate (1 per cent) at pH 7.5.

STERILIZATION Collings, Remington, Hays and Drill (1940) reported that Seitz filtration produced a total loss of activity. This was not observed, however, by Battro, Braun-Menéndez, Lanari and Leloir (1940), Schales (1942), or Katz and Goldblatt (1943)

ELECTROPHORESIS. Jonnard and Thompson (1942) studied renin electrophoretically and observed that it migrated toward the cathode between pH 3.0 and 6 5 while depressor substances, present in the crude extracts, went toward the anode between pH 5 0 and 7 5. According to Katz and Goldblatt, renin migrates toward the anode at pH 7 6.

PREPARATION

Numerous methods have been described for the preparation of renin, and fairly pure extracts have been obtained It is difficult to decide what procedures have given the purest preparation since measurement of activity has been performed by various methods which lack precision

Fresh kidneys have usually been used Their freshness, however, does not appear to be important since they may be kept in the cold for more than a week without losing an appreciable amount of renin.

For preparation on a large scale, kidneys of pig, beef, or horse may advantageously be used. The first step consists of removing the medullary tissue which contains no renin. Renin may be obtained from the cortical tissue by obtaining press juice with a hydraulic press, by extracting with saline solution, or by drying with alcohol or acetone. The method of choice depends mainly upon the facilities available in each laboratory.

PRESS JUICE Hessel (1938a) apparently obtained fairly pure extracts from the juice obtained by a hydraulic press

SALINE EXTRACTION Its extraction with saline has been employed by Laufberger (1937), Pickering and Prinzmetal (1938a), Swingle, Taylor, Collings and Hays (1939), Braun-Menéndez, Fasciolo, Leloir and Muñoz (1940a) This last method is described in the Appendix

The method of Collings, Remington, Hays and Drill (1940) by which good preparations may be obtained, is as follows: Ten liters of 2 per cent saline are mixed with 3 kgm of frozen renal cortex. With unfrozen kidneys the yield appears to be less. It is left for 24 hours under toluol and the solid part is separated, first by straining through cloth and then by Sharples centrifugation The pH is adjusted to 4 5 and the solution is allowed to stand for 12 to 24 hours. The solids are then removed by centrifugation and filtration, and the pH of the filtrate adjusted to 6 8 It is concentrated *in vacuo* to a volume of 1 liter, the temperature being kept below 45°C. The solution is then filtered through Hiflo-supercell To the filtrate are added 100 gm. of sodium chloride and the pH is adjusted to 2. It is filtered through Hiflo-supercell and the precipitate is suspended in two liters of water The pH is raised to neutrality and the solution

is stirred by a motor stirrer for 30 minutes and filtered. The filtrate is saturated with sodium chloride and made acid to pH 2 *The precipitate* is dissolved in 500 cc of 0.1 M acetate buffer at pH 5. It is then filtered. At this stage, two lots of 3 kgm. are combined and the *solution is precipitated with ammonium* sulfate at 0 4 saturation This precipitation with ammonium sulfate is repeated five times, reducing on each occasion the volume of buffer: 500, 400, 300, 200, and 100 cc. The solids from the last precipitation are separated by centrifugation The supernatant should be colorless. If the precipitate does not dissolve easily in a volume of 40 to 70 *cc. of water to give* a clear light amber solution, the precipitation is repeated. The solution is then dialyzed against water at 6°C. and the inactive precipitate which may appear is removed This solution may be kept frozen or may be dried from the frozen state.

Katz and Goldblatt (1943) published a method with which probably the purest renin to date has been obtained. It consists of extracting kidneys, which have been previously frozen and ground up, *with dilute sodium hydroxide A pH of 7.8 is maintained at* 0 5°C. for 18 hours After separating the solid part, trichloracetic acid is added to a pH of 2.8 ± 0 05. This solution is left overnight at 0 5°C and then filtered and dialyzed The dialysis sacs are left for 24 hours in front of a fan in order to reduce the volume to one-fifth of the original The pH is raised to 6, a half volume of acetone added, and the solution filtered To the filtrate is again added the same quantity of acetone After 24 hours it is filtered and the active precipitate washed with 50 per cent acetone. All these steps are carried out in the cold. The precipitate is dissolved in water, dialyzed, and centrifuged. The supernatant is adjusted to pH 4 6 and an equal volume of 50 per cent alcohol added. The renin is precipitated A final fractionation with ammonium sulfate is carried out.

EXTRACTION WITH ALCOHOL OR ACETONE was used by [illegible]

met [illegible]

and Harrison (1939), and others

Schales (1942) devised a method with which he obtained a renin of considerable potency although it contained hypertensinase (Dexter and Haynes, personal communication) The dry powder obtained with acetone is extracted with 2 per cent sodium chloride and then

left for 10 to 15 hours at pH 4 2 to 4.3 in the icebox. After separating the inactive precipitate, the solution is dialyzed at 4°C. for 40 hours. After filtering, the filtrate is saturated with sodium chloride at a pH of 4 3 The active precipitate is dialyzed and filtered. It is then fractionated with ammonium sulfate between 0 33 and 0 46 saturation and dialyzed.

HUMAN RENIN

Some investigators have found it difficult to obtain human renin free from hypertensinase In our laboratory, we use the following technique with which Dexter (personal communication) has also obtained good results. To the solution which has been partially purified by precipitation with ammonium sulfate sodium chloride to 25 per cent saturation is added After solution has taken place, it is left overnight in the icebox It is then filtered through muslin and the salt crystals are removed, and to the solution is added hydrochloric acid to pH 2 to 2 5 It is filtered with Hiflo-supercell The precipitate is suspended in water, and neutralized with sodium hydroxide as it is being dissolved It is important to add the salt before the acid, because otherwise a rapid inactivation is produced

Dexter, Haynes and Bridges (1945) have described a method of preparing hypertensinase-free human renin by aqueous extraction of kidneys, precipitation of inert proteins with trichloracetic acid and sodium chloride at pH 2 9, raising the pH to about 5, precipitation of the renin with ammonium sulfate, and dialysis

CHARACTER OF THE REACTION BETWEEN RENIN AND HYPERTENSINOGEN

Pressor activity arising from the reaction between renin and hypertensinogen varies with the amount of hypertensinase contained in the solution If the amount of hypertensinase is great, hypertensin does not accumulate in sufficient amounts to measure With less amounts of hypertensinase, hypertensin is at first detectable but after a time it disappears This type of reaction (figure 36) was described by Braun Menéndez, Fasciolo, Leloir and Muñoz (1940a) and by Page and Helmer (1940a) The interpretation given by the latter investigators was that renin, itself, continued to act and finally destroyed the hypertensin

INFLUENCE OF THE AMOUNT OF RENIN. Using solutions free from hypertensinase, Muñoz, Braun-Menéndez, Fasciolo and Leloir (1940) (figure 37) observed that hypertensin once formed did not disappear. When the concentration of renin was increased, a maximum yield of hypertensin was soon obtained which corresponded to the complete transformation of hypertensinogen With lower concentrations of renin, the maximum yield of hypertensin was reached only after more prolonged incubation. Plentl and Page

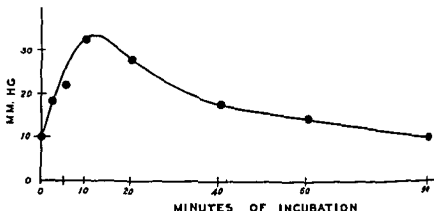


FIGURE 36 FORMATION OF HYPERTENSIN IN SOLUTIONS CONTAINING HYPERTENSINASE

Blood pressure increases produced by acetone extracts from ten cc. of blood globulins (equivalent to 20 cc. serum) incubated at 37°C with 0 25 cc. renin (equivalent to one gm fresh kidney) for various times Note the gradual reduction of pressor activity (After Braun Menéndez, Fasciolo, Leloir and Muñoz, J Physiol, *1940, 98, 283*).

(1943a, b) repeated these experiments in greater detail. It is to be noted, however, that they calculated the amount of hypertensin formed by the following equation: Units in the unknown sample equal rise of pressure produced by the unknown divided by rise of pressure obtained from one unit of standard hypertensin (angiotonin) This procedure gives correct results only when approximately the same amount of hypertensin is present in both the unknown and the standard solution. They obtained curves which correspond fairly well to those calculated by the equation for monomolecular reaction ($-\frac{dP}{dt} = KP$) where P represents the concentration of hypertensinogen. It is to be noted, however, that the formula for

bimolecular reactions (figure 38) also gives similar curves.

Plentl and Page suggested expressing renin concentration in terms of the reaction constant instead of arbitrary units. This is perfectly acceptable but more laborious and we believe it offers no advantages.

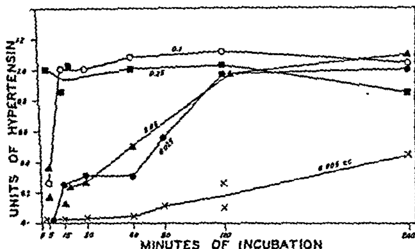


FIGURE 37 FORMATION OF HYPERTENSIN IN SOLUTIONS CONTAINING NO HYPERTENSINASE

Units of hypertensin formed by incubating 10 cc. of bovine plasma—treated so as to destroy hypertensinase [illegible]

[illegible]

Leloir, Am. J. M. Sc., 1940, 200, 608)

INFLUENCE OF THE AMOUNT OF HYPERTENSINOGEN. When the amount of hypertensinogen is varied and the amount of renin is kept constant and in excess, an amount of hypertensin is obtained which is proportional to the amount of hypertensinogen added (See determination of hypertensinogen, Chapter V).

When small amounts of renin are used, variations in the concentration of hypertensinogen do not appear to influence the velocity of the reaction (figure 39). It will be noted that the differences in concentration studied were not great since pure serum was compared with serum diluted one to two times These differences in

concentration, however, were well within the physiologic range.

In a number of enzyme reactions, it has been observed that when the concentration of substrate is increased in comparison with that of the enzyme, the velocity of the reaction is unaffected by changes in the concentration of substrate This appears to be true of the reaction between renin and hypertensinogen, in which the evidence suggests that renin acts at maximal velocity The concentration of hypertensinogen in the reactions studied has been low and the con-

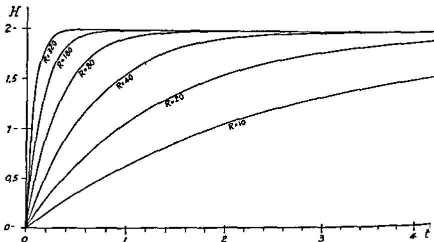


Figure 38 Curves Obtained by Applying the Formula for Bimolecular Reactions to the Renin-Hypertensinogen Reaction

The equation $\frac{dH}{dt} = K\ (R\text{-}H)\ (P\text{-}H)$ integrated gives $t = \frac{K'}{R\text{-}P} \log \frac{P\ (R\ H)}{R\ (P\ H)}$.
Taking $K' = 0\ 36$, P (hypertensinogen) = 2, R (renin) varies between 10 and 320, H (hypertensin) in ordinates, and t (time) in abscissas.

centration of renin must have been extremely small. Even if we do not accept this, we have to admit that the velocity of reaction between renin and hypertensinogen is relatively slow.

The curves of formation of hypertensin obtained by Plentl and Page (1943a) indicated that the velocity of the reaction was proportional to the decrease in concentration of hypertensinogen. It is difficult at the moment to reconcile these results with those just mentioned

OPTIMAL pH. The optimal pH of the reaction between renin and

hypertensinogen was studied by Muñoz, Braun-Menéndez, Fasciolo and Leloir (1940) The maximal rate of formation of hypertensin was obtained between pH 7.5 and 8 5 (figure 40).

RENIN AS AN ENZYME Muñoz, Braun-Menéndez, Fasciolo and Leloir (1939) suggested that renin is an enzyme All evidence at this

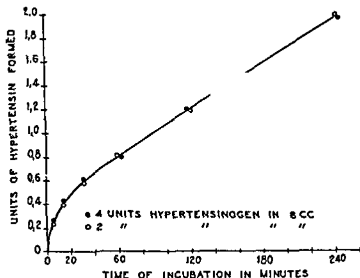


FIGURE 39 FORMATION OF HYPERTENSIN WITH DIFFERENT CONCENTRATIONS OF HYPERTENSINOGEN

Hypertensin formed by incubation of one unit of pig renin with hypertensinase free beef plasma at 37°C It is to be observed that within the variation of concentration of hypertensinogen employed, there is no difference in the amount of hypertensin formed (After Taquini, Braun-Menéndez, Fasciolo, Leloir and Muñoz, Rev Soc argent de biol, 1943, *19*, 500)

time confirms their hypothesis It is known that the two nondialyzable substances, renin and hypertensinogen, give rise to hypertensin which is dialyzable

Renin + hypertensinogen = hypertensin + X, where X may be one or several substances The molecular weight of hypertensinogen is probably in the order of 150,000, since it is a serum globulin. As regards hypertensin, its molecular weight appears to be somewhere between 400 and 1,000 as indicated by preliminary measures of its

velocity of diffusion. If X were a single substance, its molecular weight would have to be extremely high.

It is generally considered that a reaction is enzymatic when it satisfies the following conditions: (1) there is a specificity of reaction; (2) there is an optimum of pH and of temperature; (3) the amount of

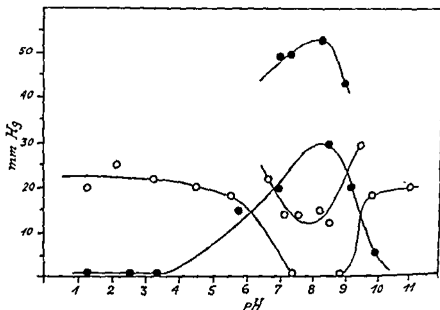


FIGURE 40 pH ACTIVITY CURVE OF RENIN AND HYPERTENSINASE

Black dots blood pressure increases produced by injecting the extract of ten cc blood globulin solution incubated with 0 25 cc. renin for fifteen minutes Each curve corresponds to one experiment. White dots: lower curve. extracts from ten cc. ox-blood plasma incubated 80 minutes with 0 5 cc. hypertensin solution Upper curve. another experiment with 50 minutes' incubation Reaction temperature 37°C. pH adjusted with HCl or NaOH and measured in an aliquot part with a glass electrode (After Muñoz, Braun-Menéndez, Fasciolo and Leloir, Am J M Sc, 1940, *200*, 608).

substrate transformed is much greater than the amount of enzyme needed. The specificity and optimum of pH and temperature of enzymatic reactions are undoubtedly due to the protein nature of the enzyme and are probably concerned in all protein reactions The quantitative relation between enzyme and substrate transformed has not been demonstrated in the case of the reaction between renin and hypertensinogen since at the moment we have no data concerning

the amount of active material contained in the impure solutions which we call renin, hypertensinogen, and hypertensin.

Indirect evidence further supporting the belief that renin is an enzyme is that pepsin, a known enzyme, acts upon hypertensinogen to form a pressor substance (pepsitensin) which is quite similar to hypertensin.

If the reaction should be carried out between one molecule of renin and one molecule of hypertensinogen, curves similar to those published by Muñoz and collaborators (1940) can be obtained by applying the equation for a bimolecular type of reaction: hypertensinogen + renin = hypertensin + other substances (figures 37 and 38)

It may be concluded that although there is strong evidence for the belief that renin is an enzyme, there is still a remote possibility that it represents a bimolecular type of reaction.

If the reaction is enzymatic, there is no doubt that the substrate is hypertensinogen since it is only by increasing the amount of renin that the transformation of the hypertensinogen molecule to hypertensin is accelerated (see action of pepsin, Chapter XI).

CHEMICAL CHANGES PRODUCED IN THE REACTION BETWEEN RENIN AND HYPERTENSINOGEN Braun-Menéndez, Fasciolo, Leloir and Muñoz (1940a) observed that fairly impure solutions of renin were capable of causing proteolytic breakdown of solutions of hemoglobin under the conditions described by Anson (1938) In a later work, Leloir, Muñoz, Braun-Menéndez and Fasciolo (1940a), using more purified renin, observed that the proteolytic activity measured in this way was not parallel to the activity of the formation of hypertensin They concluded that this procedure did not serve as a method for the measurement of renin Croxatto and Croxatto (1941a) observed an increase of nonprotein nitrogen by incubating renin with hypertensinogen. There was at first an increase of nitrogen precipitable by phosphotungstic acid which the authors attributed to the formation of hypertensin Later, this became diminished while the nitrogen which was not precipitable by phosphotungstic acid increased They attributed this change to the digestion of *hypertensin* by *hypertensinase*. These authors used impure solutions of renin and did not demonstrate that the nitrogen which they

measured corresponded to the hypertensin formed in the reaction or to its breakdown products

In our laboratory, numerous attempts have been made to discover some chemical change in the reaction, but all, including the determination of nitrogen, have failed to the present time due to an inability to detect such minute differences as occur. Those changes which have been detected have likewise been present in control experiments.

METHODS FOR THE MEASUREMENT OF RENIN

Renin can be measured (1) by direct intravenous injection; (2) by measurement of the hypertensin formed *in vitro;* and (3) by measurement of the hypertensinogen which it is capable of destroying *in vitro* in a given time.

(1) DIRECT INTRAVENOUS INJECTION. Pickering and Prinzmetal (1938a) were the first to define a unit of measure of renin Their unit was defined as the amount necessary to elevate the blood pressure of a rabbit 20 to 30 mm Hg, the blood pressure being measured in the artery of the ear Swingle, Taylor, Collings and Hays (1939) studied the proportionality between action and dose of renin injected intravenously into dogs anesthetized with nembutal. The unit was defined as the amount which when administered to dogs intravenously over a period of two to five seconds elevated the blood pressure by an average of 40 mm Hg.

In a later work, Remington, Collings, Hays and Swingle (1940) stated that with large doses of renin the pressor response varied with the initial blood pressure, while with smaller doses the response was much more regular. They recommended the use of small amounts of renin and tested them several times in two or three dogs anesthetized with nembutal

Wakerlin and Chobot (1939a) preferred to use nephrectomized dogs which are more sensitive to the action of renin.

Schales and Haynes (1941) defined a rabbit unit as the amount per kilogram of body weight which when injected intravenously into four rabbits produced an average rise of 30 mm. Hg pressure. They observed that pig renin produced the same elevation in the dog as in the rabbit when the same amount was injected per kilogram of body weight.

According to Goldblatt, Katz, Lewis and Richardson (1943), the pressor response bears no relation to the body weight of dogs of 10 to 25 kgm. They defined the dog unit as the amount which raised the blood pressure 30 to 35 mm Hg within three minutes of its intravenous injection Measurements were made on at least three unanesthetized dogs.

An important drawback of these methods is their lack of specificity since many substances are capable of elevating blood pressure Unless the blood pressure curve is sufficiently characteristic for renin, it is difficult at times to differentiate it from other substances Tyramine and pitressin, for example, produce similar curves.

A further disadvantage is the variability of response of different animals, some giving a greater rise than others Since the phenomenon of tachyphylaxis prevents the comparison with a solution of known potency, it is difficult to obviate this drawback If the average pressure rise of several animals is taken, good results are obtainable This method is not applicable for the study of physiologic amounts of renin

(2) METHODS BASED ON THE AMOUNT OF HYPERTENSIN FORMED: DIRECT METHOD This method was devised by Leloir and collaborators (1940a) for the qualitative detection of renin in the venous blood of ischemic kidneys Kohlstaedt and Page (1940a) and Page (1940a) employed a method by which the presence of hypertensin was detected by its vasoconstrictor action on the rabbit's ear Since perfusion of the rabbit's ear as well as perfusion of the hind limb of a frog (Lawen-Trendelenburg) gives unreliable results, due to a lack of specificity and reproducibility, Leloir and collaborators (1940b) introduced a method for assaying hypertensin by recording the pressor response produced in the dog This method is accurate and permits an easy comparison with a solution of hypertensin of known potency Dexter, Haynes and Bridges (1945) have applied this method satisfactorily in cats, and Soaje-Echague (1944) in rats.

Renin may readily be quantitated in terms of the amount of hypertensin to which it gives rise under controlled conditions The various factors which influence the formation of hypertensin must be controlled These include time of incubation, pH, temperature, and concentration of hypertensinogen. Hypertensinase must be eliminated from the solutions The destruction of hypertensinase is the

most difficult part of the technique since renin is easily destroyed in the process.

By acidifying to a pH of 3.8 ± 0.1, hypertensinase is first destroyed, then hypertensinogen, and finally renin. At 17°C. the hypertensinase disappears entirely in one hour, and at 25°C. in 20 *minutes. Under the latter conditions*, hypertensinogen is unaltered. By incubating for 30 minutes at 37°C. at this pH, both hypertensinase and hypertensinogen are entirely destroyed while renin is unaffected.

These data apply to pig renin and beef hypertensinogen. Renins from other animals have not been studied. Human renin appears to be *destroyed with greater facility than that of pig according to* Dexter, Haynes, and Bridges (1945) who devised the following method for ridding human plasma of its hypertensinase without affecting the renin: *To 30 cc. of human serum or plasma at 5°C. are added* 2.7 gm. (90 gm. per liter) of solid sodium chloride and a few drops of toluol as a preservative. The pH is lowered to 2.0 (glass electrode) with 10 per cent hydrochloric acid and left for 2 hours at 5°C. Whereas the hypertensinase is destroyed by this procedure, the renin remains unchanged. The pH is raised to between 5 and 6 with *N* sodium hydroxide and the solution is dialyzed in a cellophane sac overnight against water at 5°C. The contents of the sac are removed and divided into 3 equal parts. To each is added an excess (*6 to 8 cc.*) of hypertensinase-free beef hypertensinogen (prepared as described in the Appendix), 0.5 cc. $\frac{M}{2}$ phosphate buffer at pH 7.3, and 0.2 cc. 1:1000 merthiolate (Lilly). The first tube is incubated for 4 hours at 37°C., the second is unincubated, and the third is incubated for 4 hours at 37°C. with enough hemolyzed fresh human red blood cells (blood hypertensinase) to produce a faint pink color. At the end of incubation, the reaction is stopped and the proteins precipitated by heating for 5 minutes in boiling water and adding 3 volumes of 95 per cent alcohol. The remainder of the procedure is identical with that described in the Appendix.

The unit of renin is defined as the amount which produces 0.5 unit of hypertensin in two hours under the conditions described. Leloir, Muñoz, Braun-Menéndez and Fasciolo (1940b) published results which showed the usefulness of the method. The technique for the assay of renin is described in the Appendix.

The specificity of the method is undoubtedly greater than that by direct injection. If preformed pressor substances such as tyramine and pitressin are present, they are detected in the unincubated control tube of plasma No known substance other than renin produces a pressor agent under the conditions described above

The accuracy of the method depends upon the precision with which hypertensin is measured In a good dog, an accuracy within 10 per cent can be obtained, but with other dogs greater errors may occur. It is therefore wise to make all measurements in duplicate.

Causes of error are numerous If the pH during the destruction of hypertensinase is too low, the renin may be destroyed. If it remains too high, it does not destroy all the hypertensinase. Under these conditions the hypertensin which is formed later during incubation is partially or entirely destroyed The pH during the incubation with hypertensinogen must be well controlled since renin has an optimal pH between 7 5 and 8 5 Contamination with microorganisms may destroy hypertensin if the incubation is prolonged This danger may be avoided by using appropriate antiseptics.

The final precipitation of the proteins from the solution with alcohol is laborious since it necessitates a distillation under reduced pressure in order to remove the alcohol. We have found it, however, to be more satisfactory than other methods tried The removal of the proteins with heat and acidification leaves substances in the filtrate which often possess a depressor effect on being injected into the assay animal. The removal of proteins with dilute trichloracetic acid has the disadvantage of producing losses of hypertensin and necessitates several extractions with ether in order to eliminate the trichloracetic acid.

The sensitivity of the method is some 50 to 200 times greater than that of direct injection The unit which Leloir and collaborators (1940b) defined was some 100 times smaller than that of Swingle and collaborators (1939)

(3) METHOD BASED ON DIMINUTION OF HYPERTENSINOGEN. INDIRECT METHOD In this procedure, the amount of hypertensinogen which disappears as a result of the action of renin is measured (Leloir and collaborators, 1940b) In order to do this, renin is incubated with hypertensinogen in the presence of hypertensinase Through the action of renin, the hypertensinogen de-

creases as hypertensin is formed. If the incubation is sufficiently prolonged, the hypertensin formed is destroyed by the hypertensinase. If the hypertensinogen is measured before and after incubation, there will be a difference which is proportional to the amount of renin

This method is extremely sensitive. In order to detect minute amounts of renin, prolonged periods of incubation may be used, due precautions being taken to avoid bacterial contamination

One advantage of the indirect over the direct method is the elim-

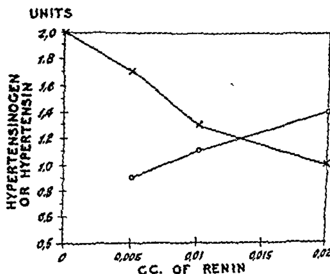


FIGURE 41. COMPARISON OF THE DIRECT AND INDIRECT METHODS FOR THE ASSAY OF RENIN

of
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Braun-Menéndez and Fasciolo, Rev. Soc argent. de biol, 1940, *16*, 635).

ination of the difficult step of destroying hypertensinase. Since the presence of renin is recognized by differences in the amount of hypertensinogen present with and without incubation, the error is greater than that of the direct method. Results obtained by these two methods are shown in figure 41.

Measurement of Human Renin by the Indirect Method Human renin acts upon human, beef, and horse hypertensinogen, while that of pigs acts on the latter two but not on human hypertensinogen (see specificity of renin). This fact led Muñoz, Braun-Menéndez, Fasciolo,

Leloir and Taquini (1943) to devise the indirect method for the measurement of human renin. A measured amount of beef hypertensinogen is added to human serum containing human renin After a period of incubation in the presence of hypertensinase, pig renin is added in order to measure the beef hypertensinogen which remains The difference between the amount of beef hypertensinogen before and after incubation gives a measure of the amount of human renin (for details of the method, see Appendix)

Various factors which may influence the reaction have been studied. It has been shown that if certain precautions are taken to avoid bacterial contamination, beef hypertensinogen does not disappear in incubation periods lasting 15 hours at 39°C Beef and horse hypertensinogen are better than that of the dog because the latter appears to be more slowly acted upon by human renin. The amount of hypertensinase necessary for the complete destruction of hypertensin without interfering with the measurement of the amount of beef hypertensinogen was also determined.

One unexpected finding was that human renin acted equally well on beef hypertensinogen regardless of whether or not an excess of human hypertensinogen was present. It had been anticipated that when human renin was incubated with both hypertensinogens, less beef hypertensinogen would disappear

The advantages of the indirect method are as follows (1) It permits the detection of amounts of renin somewhat less than that by the direct method, (2) it is unnecessary to destroy hypertensinase which is a difficult step in the direct method especially in the case of human renin which appears to be more labile than that of pigs

Disadvantages of the indirect method are first that the measurement is made by determining the difference between two samples whereby there may be a summation of errors. Using about 0 5 unit of hypertensinogen, this difficulty is in part avoided and the measurement is more exact Second, there is the possibility that in the sample there may be substances other than renin which are capable of destroying hypertensinogen

SPECIFICITY OF RENIN

IN VITRO EVIDENCE Fasciolo, Leloir, Muñoz and Braun-Menéndez (1940a) observed that human renin was capable of producing hypertensin by acting on the plasma of human beings, pigs, dogs,

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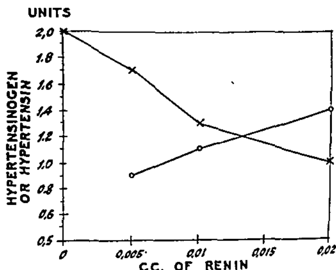


FIGURE 41 COMPARISON OF THE DIRECT AND INDIRECT METHODS FOR THE ASSAY OF RENIN

The line with circles shows the formation of hypertensin with different amounts of renin The line with crosses shows the amount of hypertensinogen not transformed to hypertensin Incubation for two hours at 37°C (After Leloir, Muñoz, Braun-Menéndez and Fasciolo, Rev Soc argent de biol, 1940, *16*, 635)

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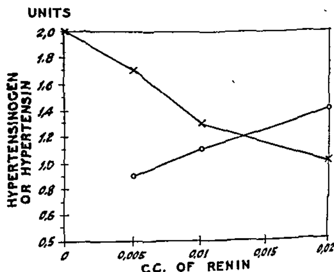


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It was shown that pig renin produced no change in human hypertensinogen when it was incubated with it. Thus, if pig renin was incubated with human hypertensinogen, the latter lost no capacity of forming hypertensin when subsequently incubated with human renin.

Pig renin lost none of its activity when incubated with human plasma The apparent specificity of the reaction between renin and human hypertensinogen was confirmed in later investigations in which the reaction was studied in other species The results obtained *in vitro* are shown in table 1.

The only renins capable of acting on human hypertensinogen are those of primates Renins from other mammals, however, act upon the serum of other species Renin of the chicken acts only upon chicken serum and possibly upon that of the duck In reptiles, batrachians and fish it would appear that the renin-hypertensinogen system has not been developed for the regulation of blood pressure

Experiments performed up to the present have not been more than qualitative, and it is possible that a more careful investigation would show differences in the velocity of reaction between different renins and different hypertensinogens

IN VIVO EVIDENCE The action of different renins has also been investigated by direct injection This is not as accurate a procedure as the *in vitro* techniques since extracts may contain extraneous pressor substances It has been observed, however, that pig renin produces a rise of pressure in dogs but not in man, and that human renin produces a rise in man (table 2)

In dogs, a rise of pressure is produced with renal extracts from man, dog, beef, sheep, pig and dolphin but not with chicken renin Chickens and ducks react with chicken renin but with no others.

The toad and the serpent do not react to any renin

As regards fish renin, Bean (1942a) investigated renal extracts of sharks (elasmobranchs) One part of the kidney of these fish consists mainly of glomerular tissue and another predominantly of tubular tissue. Extracts of both portions were injected into dogs without producing rises of blood pressure. Friedman and Kaplan (1942) obtained rises of blood pressure in dogs with renal extracts of carp (Cyprinus carpio), and of catfish (Ameiurus nebulosus) which are fresh water fish with glomerular kidneys Marine fish with glomerular

TABLE I PRODUCTION OF HYPERTENSION "IN VITRO" WITH RENIN AND SERUMS OF DIFFERENT ANIMALS

Renin	Serums													
	Man	Baboon	Monkey	Ox	Horse	Hog	Sheep	Dog	Cat	Rabbit	Rat	Chicken	Toad	Shark
Man	+ 1–4	+ 4	+ 4	+ 1	+ 1	+ 1		+ 1				− 2		
Baboon	+ 5	+ 5	+ 5											
Monkey	+ 5	+ 5	+ 5											
Ox	− 3			+ 3				+ 3				− 2		
Horse														
Hog	− 1–4	− 4	− 4	+ 1	+ 1	+ 1		+ 1			+ 3	− 2	− 2	
Sheep	− 3–4	− 4	− 4	+ 3			+ 2	+ 3				− 2		
Dog	− 3–4	− 4	− 4	+ 3				+ 3						
Cat	− 4	− 4	− 4											
Rabbit	− 4	− 4	− 4											
White Rat				+ 3										
Chicken				− 2				− 2				+ 2	− 2	− 2
Toad				− 2				− 2				− 2	− 2	− 2
Shark				− 2				− 2				− 2	− 2	− 2

1. Fasciolo, Leloir, Muñoz and Braun-Menéndez, 1940a.
2. Bean, 1942a, b
3. Unpublished experiments
4. Corcoran, Helmer and Page, 1942.
5. Corcoran, 1943.

horses, beef and goats. Pig renin, on the other hand, produced no hypertensin when it was incubated with human serum, although hypertensin was formed if it acted upon the other plasmas mentioned above.

kidneys contained no renin (Kaplan and Friedman, 1942). No rises of pressure were obtained with renal extracts of an aglomerular fish (Porichytys notatus). These experiments should be supplemented with *in vitro* studies in order to be conclusive. It would be extremely interesting if renins derived from such different species should be active in the dog (see Chapter VIII).

Landis, Jeffers and Shiels (1940) prepared renal extracts by heating to 55 to 56° C for 20 minutes By this method of extraction, active extracts were obtained as judged by rises of pressure obtained Doubt exists, however, for the applicability of this method to the preparation of human kidneys since they obtained little activity in most of their preparations They administered rabbit renal extract weekly to rabbits, and noted continued pressor responses, while with renal extracts from other species, anaphylactic disturbances were produced after a time These disturbances might be attributed either to heterologous renin or to other proteins contained in the extracts They found that rats and guinea pigs were more sensitive than dogs and rabbits when the same amount was administered per kilogram of body weight In this regard it will be recalled that Schales (1942) showed that dogs were some twenty times more sensitive to human renin than rabbits

ACTION OF RENIN ON THE CARDIOVASCULAR SYSTEM

The intravenous injection of renin produces many effects in man and animals Renin transforms the hypertensinogen into hypertensin At the present time, no pharmacologic action of renin is known which can not be explained by the formation of hypertensin The pharmacology of these two substances is therefore the same in the majority of cases

PRESSOR ACTION Tigerstedt and Bergman (1898) discovered renin by its pressor action This property has been amply confirmed by many investigators

ROUTES OF ADMINISTRATION An increase of pressure is produced when renin is injected either into the artery or into the vein These are the routes most used since the injected renin reaches a concentration in the blood sufficient for its pressor action to appear.

TABLE II PRESSOR ACTION OF RENAL EXTRACTS FROM DIFFERENT ANIMALS

Renal Extract	Animal Receptor									
	Man	Dog	Cat	Rabbit	Guinea Pig	Rat	Chicken	Duck	Toad	Snake
Man	+ 1–4–5	+ 6					− 2	− 2	− 2	− 2
Dog		+ 7					− 2	− 2	− 2	− 2
Ox		+ 6								
Hog	− 1–4–5	+ 7	+ 7	+ 7		+ 7	− 2	− 2	− 2	− 2
Sheep		+ 2					− 2	− 2	− 2	− 2
Rabbit				+ 7–9	+ 9	+ 9				
Guinea pig		+ 9		+ 9	+ 9	+ 9				
Rat		+ 9				+ 7–9				
Dolphin		+ 3								
Chicken		− 2					+ 2	+ 2	− 2	− 2
Toad		− 2					− 2	− 2	− 2	− 2
Fish: Shark		− 2					− 2	− 2	− 2	− 2
Fish: Cod		− 10								
Fish: Flounder		− 10								
Fish: Carp		+ 8								
Fish: Catfish		+ 8								

1 Battro and collaborators (1940)
2 Bean (1942a, b)
3 Eichelberger, Leiter and Geiling (1940)
4 Schales, Hoobler and Haynes (1941)
5 Turnoff and Rowntree (1941)
6 Unpublished experiments
7 Several authors
8 Friedman and Kaplan (1942).
9 Landis, Jeffers and Shiels (1940)
10 Kaplan and Friedman (1942).

into the blood stream. Burlingame, Long and Ogden (1942) found that when tachyphylaxis was produced in the mother rat, it was not observed in the fetus This might be explained by the failure of renin to pass to the fetus *Tachyphylaxis is not an exclusive property* of renin It is also observed with other drugs such as pitressin, veritol, and ephedrine Apparently this phenomenon is analogous to the progressive reduction of response observed in muscular fatigue. Extensive studies of this phenomenon, however, have demonstrated that tachyphylaxis is due to other mechanisms It has been observed, for example, that pressor amines of the adrenalin group (sympathol, cobephrin) which are rapidly destroyed, give no tachyphylaxis Ephedrine and veritol, on the other hand, produce tachyphylaxis. They are more stable because their molecule contains only one or no phenolic groups It seems reasonable to conclude that substances with greater stability remain for a longer time in the organism, acting upon specific receptors and thereby preventing further action from new injections

With renin, the mechanism of tachyphylaxis appears to be different. As we have seen, its pressor action is due to the formation of hypertensin from the transformation of hypertensinogen. Successive injections of renin produce a progressive diminution in the concentration of hypertensinogen in the plasma. When the latter becomes exhausted, a new injection of renin produces no effect (Page, 1939a) A result similar to that with repeated doses can be obtained by the single injection of a large dose Houssay, Braun-Menéndez and Dexter (1942) showed that renin remained in the blood stream for at least 30 minutes after the injection of 80 to 120 units During this time, hypertensinogen was being transformed into hypertensin This led to a reduction of hypertensinogen resulting in the appearance of the phenomenon of tachyphylaxis It may be concluded that renin tachyphylaxis is due to the persistence of renin in the blood and to the exhaustion of hypertensinogen It is possible, however, that some other mechanism may influence the production of this phenomenon Wakerlin and Johnson (1940) reported an elevation of blood pressure in three of 28 dogs in a state of tachyphylaxis produced by dog renin by the injection of rabbit renin The number of positive results presented by these investigators does not permit definite conclusions to be drawn

Freedman (1940) obtained rises of pressure in unanesthetized rats by administering renin intraperitoneally.

LATENT PERIOD. The pressor effect of renin becomes manifest some 15 to 20 seconds after its injection.

FORM OF THE CURVE. As can be seen in figure 42, the rise is gradual, the height and duration of the curve being proportional to the dose injected. The fall is gradual and is not followed by hypotension Persistence of the pressor action varies with the amount injected and can be observed to last 30 or 40 minutes or more.

RESPONSE TO REPEATED INJECTIONS–TACHYPHYLAXIS

When repeated injections are made at short intervals, it is observed that the pressor response is each time less; finally no response *is obtained despite the injection of large doses (figure 42).* This

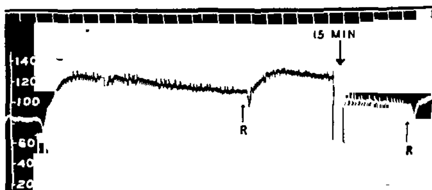


FIGURE 42 TACHYPHYLAXIS TO RENIN

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phenomenon has been called tachyphylaxis It was observed by Tigerstedt and Bergman (1898) and has since been studied by numerous investigators [1] Tachyphylaxis appears when renin is injected directly

[1] Bingel and Strauss, 1909, Hessel, 1938a; Pickering and Prinzmetal, 1938a; Swingle, Taylor, Collings and Hays, 1939, Page, 1939a; McEwen and Harrison, 1939, McEwen, Harrison and Ivy, 1939, Page and Helmer, 1940b; Katz and Goldblatt, 1943, and others

increase after nephrectomy and its diminution after adrenalectomy (see Chapter V) perhaps explain the differences observed in the response to renin.

The age of animals appears to influence the sensitivity to renin. Grossman and Williams (1938) injected rats of different ages with amounts of renin proportional to the body surface. The pressor rises obtained were inversely proportional to the age of the animal, being greatest in the young and least in the elderly Adrenalin produced similar rises in all the animals Candiani and Croxatto (1944) reported that the subcutaneous or intraperitoneal injection of 10 to 50 units of aminopolypeptidase before or simultaneously with an injection of renin prevented the usual pressor effect of renin Cruz Coke (1945) found that the reaction between renin and hypertensinogen was inhibited by methylnaphthoquinone and that this inhibition was preventable by the addition of ascorbic acid Dalton and Nuzum (1944) reported that sodium thiocyanate injected subcutaneously or given by mouth reduced the pressor effect of a renin-like substance injected intraperitoneally into normal dogs

ACTION OF DRUGS The pressor action of renin is not abolished by ergotamine,[5] Fourneau 933,[6] atropine,[7] or nicotine [8] According to Williams (1938) ergotamine inhibits the action of renin in the rat.

Cocaine, which prevents the action of tyramine, has no inhibiting action on renin according to Friedman, Abramson and Marx (1938), Abramson and Friedman (1938), Hessel (1938b), and Page (1939a) Its action is somewhat enhanced according to Muñoz, Braun-Menéndez, Fasciolo and Leloir (1940), and definitely so according to Williams (1938)

Ether anesthesia diminishes its action in rabbits (Pickering and Prinzmetal, 1938a, Scarff and Martin, 1941) The same is true of urethane and nembutal anesthesia according to Pickering and Prinzmetal (1938a)

[5] Friedman, Abramson and Marx, 1938, Hessel, 1938b, Page, 1939a, Helmer and Page, 1939, Swingle, Taylor, Collings and Hays, 1939

[6] Katz and Friedberg, 1939, Muñoz, Braun-Menéndez, Fasciolo and Leloir, 1940, Leo, Prinzmetal and Lewis, 1940

[7] Hessel, 1938b, Friedman, Abramson and Marx, 1938, Page, 1939a, Muñoz, Braun Menéndez, Fasciolo and Leloir, 1940

[8] Hessel and Maier Husser, 1934

CONDITIONS WHICH MODIFY THE PRESSOR ACTION OF RENIN

The pressor action of renin is not modified by section of the vagi or of the splanchnics, by denervation of the carotid sinus (Page, 1939a; Muñoz, Braun-Menéndez, Fasciolo, and Leloir, 1940), by destruction of the central nervous system,[2] or by decapitation (Merrill, Williams and Harrison, 1938a) According to Euler and Sjostrand (1941a), cervical or lower bulbar section causes a sharp reduction in the pressor action of renin

According to Burlingame, Long and Ogden (1942), the injection of renin to rats at the end of pregnancy did not modify the fetal blood pressure Larger doses produced a fall of the fetal blood pressure. When injected directly into the fetus, a rise of pressure was produced

Advance adrenal insufficiency following removal of the adrenals diminishes the pressor action of renin,[3] and the administration of cortical extracts restores responsiveness (Remington, Collings, Hays, Parkins and Swingle, 1941). Hypophysectomy, on the other hand, does not modify the response in dogs (Houssay and Dexter, 1942), but increases it in rats (Williams, Díaz, Burch and Harrison, 1939, Friedman, Somkin and Oppenheimer, 1940).

Nephrectomy increases the sensitivity to renin. This fact, first observed by Tigerstedt and Bergman (1898), was confirmed later by many investigators[4] The duration of the pressor effect of renin is also greater in nephrectomized than in normal animals (Freedman, 1940; Leiter and Eichelberger, 1943) The greater sensitivity to renin is not a constant finding although it is observed in the majority of nephrectomized animals The cause of these variations between one animal and another has not been determined.

Variations in the sensitivity of animals to renin appear to be conditioned by the amount of hypertensinogen present in the plasma Its

[2] Tigerstedt and Bergman, 1898, Bingel and Strauss, 1909, Hessel and Maier Husser, 1934, Friedman, Abramson and Marx, 1938, Page, 1939a

[3] Hessel, 1938a, Page, 1938, Williams, Diaz, Burch and Harrison, 1939, Friedman, Somkin and Oppenheimer, 1940; Remington, Collings, Hays, Parkins and Swingle, 1941, Houssay and Dexter, 1942, Soaje-Echague, 1944

[4] Merrill, Williams and Harrison, 1938a, Wakerlin and Chobot, 1939a, Page and Helmer, 1940b, Freedman, 1940, Rodbard, 1941a, b; Houssay and Dexter, 1942

Page and Helmer, 1940) When serum or blood is added to these solutions of renin, vasoconstrictor action rapidly appears. It was this action which induced Page to postulate the existence of an "activator of renin" in the serum. The presence of such a substance, however, has not been confirmed (Muñoz, Braun-Menéndez, Fasciolo and Leloir, 1939).

The rise of blood pressure is unaccompanied by any change of peripheral blood flow, according to Friedland, Kapp, and Landis (1940) and Friedman, Abramson and Marx (1938) Herrick, Corcoran

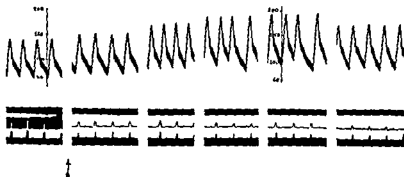


FIGURE 43. ACTION OF HUMAN RENIN ON MAN

Intra-arterial pressure in mm Hg recorded with Hamilton manometer Effect of intravenous injection of twenty cc of human renin (one cc equivalent to 10 gm of fresh kidney) Time in seconds The renin was injected at the arrow Tracings taken one, two, three, three and one half, and six minutes after the injection (After Battro, Braun Menéndez, Lanari and Leloir, Rev Soc argent de biol, 1940, *16*, 376)

and Essex (1941) observed a decrease followed by an increase, while Schales, Hoobler and Haynes (1941) observed only a slight decrease. The rise of pressure is not accompanied by a change of skin temperature of the rabbit's ear.* Friedman, Abramson and Marx (1938) reported a decrease in the volume of the limbs

Friedberg, Katz and Steinitz (1943) found that the injection of renin produced an increase of pressure in the pulmonary artery. Since they had previously observed (Steinitz and Katz, 1939) that the pressure in the pulmonary artery was unchanged in dogs with

*Landis, Montgomery and Sparkman, 1938, Corcoran and Page, 1939, Landis, Jeffers and Shiels, 1940, Kapp, Friedland and Landis, 1941

PRODUCTION OF PROLONGED HYPERTENSION WITH RENIN

If it is assumed for the moment that permanent hypertension produced by renal ischemia is due to a secretion of renin, it ought to be possible to produce permanent hypertension by repeated injections of this substance. This is a fundamental point which as yet has not been well studied. According to Hessel (1938b) repeated injections lead to a permanent elevation of the blood pressure Hill and Pickering (1939) obtained hypertension for four hours by the continuous injection of small doses After stopping the injections, the pressure fell in one to four hours. With greater doses they observed a rapid rise followed by a fall.

Other investigators have not been able to obtain prolonged hypertension (Page, 1939a; Taggart and Drury, 1940) These findings may have been due to the renin being insufficiently pure or to the use of heterologous renin or perhaps to the use of such amounts that an exhaustion of hypertensinogen was produced. This is an important point deserving further study.

ACTION OF RENIN ON MAN

The injection of pig renin does not produce hypertension in man (Battro, Braun-Menéndez, Lanari and Leloir, 1940) while the injection of human renin does produce a rise of pressure in man (figure 43) and in some mammals (Battro, Braun-Menéndez, Lanari and Leloir, 1940; Schales, Hoobler and Haynes, 1941; Turnoff and Rowntree, 1941). The rise is proportional to the amount injected and affects both systolic and diastolic pressures. In man, renin produces a reflex bradycardia, a slight diminution of blood flow to the forearm, and increase in venous pressure (Schales, Hoobler and Haynes, 1941). No change has been observed in the minute volume output of the heart.

VASCULAR ACTIONS

Renin has no direct vasoconstrictor action. When made up in Ringer's solution, renin has no vasoconstrictor action when perfused through the tail of dogs (Friedman, Abramson and Marx, 1938), through the lower extremities of the toad (Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1940a, b), or through the rabbit's ear (Kohlstaedt,

it is capable of producing a contraction of these muscles (Ludueña, 1940) (see figure 44)

ACTION ON KIDNEY According to Hessel and Maier-Hüsser (1934) renin does not produce a diuresis Corcoran and Page (1939) observed no change in the plasma clearance of urea, inulin and phenol red Wakim, Root and Essex (1941) found that renin produced no change in renal circulation of the frog either by direct application or by injection, which may well be explained by the lack of a renin-

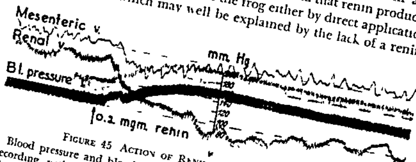


FIGURE 45 ACTION OF RENIN ON RENAL BLOOD FLOW

Blood pressure and blood flow from the renal and mesenteric veins Optical recording with the Rein thermostromuhr (After Hessel and Maier-Hüsser, Verhandl d deutsch gesellsch f inn Med, Kong, 1934, 46, 347)

hypertensinogen system in the frog (see Chapter IV) Hessel and Maier-Hüsser (1934) and Merrill, Williams and Harrison (1938b) reported that when injected into animals, renin produced changes in blood flow and renal excretion (figure 45) Corcoran and Page (1938, 1939, 1940a) observed that renin produced a reduction of renal blood flow by constriction of the efferent glomerular arteriole Pickering and Prinzmetal (1940) observed that with small doses diuresis in the rabbit was inhibited With large doses, urinary output increased without modifying the excretion of creatinine, endogenous or injected The elimination of urea was accompanied by changes similar to those observed in any water diuresis with an increase in the output of sodium and chloride A possibly related phenomenon was observed by Oster and Martinez (1943) who observed polydypsia and polyuria in hypertensive rats with renal ischemia

METABOLIC ACTIONS Hessel and Maier-Hüsser (1934) observed no changes in blood sugar Schaffer, Dill and Stander (1941),

chronic experimental hypertension, they attributed the pulmonary hypertension produced by the injection of renin to an increase in venous return to the right heart and failure of cardiac function.

ACTION ON THE HEART

In the physiologic range, renin has no significant action on the heart as Tigerstedt and Bergman (1898) first observed. The minute volume output has been described as unchanged (Somkin, 1941), or else slightly increased (Hill and Andrus, 1941). Middleton and Wiggers (1944) observed that small doses of renin and hypertensin produced insignificant changes in the systolic discharge but con-

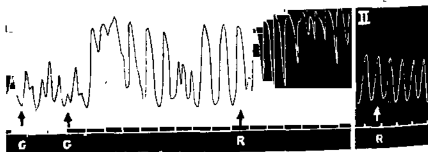


FIGURE 44 ACTION OF RENIN ON THE ISOLATED UTERUS OF THE RAT

First arrow (G), 0 1 cc of blood globulins, second arrow (G), 2 cc. of blood globulins, third arrow (R), 0 5 cc of renin At the right, fourth arrow, R, 0 5 cc of renin in another preparation. Observe that the action of renin is apparent only when blood globulins (hypertensinogen) have previously been added to the Ringer's solution Time in minutes (After Ludueña, Rev. Soc argent. de biol, 1940, *16*, 358)

comitant slowing of the heart reduced the cardiac output slightly. Doses producing a rise of 30 mm Hg. or more resulted in a variable reduction of systolic discharge and, together with slowing, reduced the cardiac output considerably.

OTHER ACTIONS OF RENIN

ACTION ON SMOOTH MUSCLES. Renin has no action on the isolated uterus (Hessel and Maier-Husser, 1934; Ludueña, 1940) It likewise has no action on the iris or melanophores (Hessel and Maier-Husser, 1934) The results obtained show *that renin, itself,* lacks any action on smooth muscles It is only in the presence of hypertensinogen, with the resulting formation of hypertensin, that

CHAPTER V

HYPERTENSINOGEN

In 1938, Kohlstaedt, Helmer and Page found that impure renin possessed a moderate vasoconstrictor action on the isolated dog's tail. This action disappeared when this substance was purified by dialysis They also observed that if the purified preparation of renin was mixed with plasma or heparinized blood diluted in Ringer's solution, the vasoconstrictor action reappeared By ultrafiltration of the plasma, they found that its ability to produce a vasoconstrictor action in combination with renin was found in the colloid part of the plasma, none being present in the ultrafiltrate These investigators believed that the vasoconstrictor action of renin was the result of its activation by a hypothetical kinase contained in plasma and in whole blood The name renin-activator was proposed for this substance by these authors

In 1939, Braun-Menéndez, Fasciolo, Leloir and Muñoz found that by incubating a mixture of renin with dog or horse renin at 37°C, a vasoconstrictor and pressor substance which they called hypertensin was formed The name hypertensinogen was given to the substance in the serum from which it arose. Almost simultaneously, Page and Helmer (1940a, c) discovered a pressor substance similar to hypertensin which they called angiotonin, which was produced by the interaction of renin and renin-activator.

Lewis and Goldblatt (1942) later suggested the terms prehypertensin and preangiotonin for the substance which, when incubated with renin, gave rise to hypertensin or angiotonin. The terms hypertensinogen, prehypertensin, preangiotonin and renin-activator are synonymous

Although Page and Helmer state that the term renin-activator indicates only that renin is inactive in the absence of this substance, it can not be denied that it suggests the idea of an activation or change in renin which actually does not take place We have therefore suggested that this term be omitted (Leloir, Muñoz, Taquini, Braun-Menéndez, Fasciolo, 1942). Recently, Page, Helmer, Plentl, Kohlstaedt and Corcoran (1943) have omitted the term renin-activa-

on the other hand, observed hyperglycemia in the Dalmatian dog In this animal, injections of renin produced an increase of uric acid in the blood together with a greater excretion of uric acid. These studies are interesting since in the Dalmatian, as in man, the metabolism of purines is different from that in other animals in that the end product is uric acid instead of alantoin.

Renin is a protein of the kidney which interacts with hypertensinogen to give rise to the formation of hypertensin. This reaction is probably enzymatic and has an optimum pH of 7.5 to 8 5, and an optimum temperature between 37 and 39°C The velocity of the reaction depends upon the amount of renin present. This latter property can be utilized for its assay. The unit of renin has been defined as that amount which when incubated with 1 to 3 units of hypertensinase-free hypertensinogen gives rise to the formation of 0 5 unit of hypertensin after 2 hours of incubation under certain conditions of pH and temperature.

Differences in the behavior of renin from different animals have been observed. Renin from man, monkey and baboon acts on the hypertensinogen of all mammals, while the renins of other mammals do not act upon the hypertensinogen of primates. Birds appear to have a renin which acts exclusively on the hypertensinogen of birds In batrachians, reptiles and fish, it would appear that there is no renin, although in fish certain contradictory results have been obtained

The pharmacologic actions of renin depend on the formation of hypertensin which is produced when renin comes in contact with the hypertensinogen of plasma. The pharmacology of renin and hypertensin are, therefore, the same in the majority of cases.

Intravenous injections of renin produce a prolonged increase of blood pressure, the duration of which is determined by its persistence in the blood

Repeated injections produce diminishing pressor responses (tachyphylaxis) which are due in part at least to the exhaustion of hypertensinogen in the blood.

One point which deserves further investigation is a study of the possibility of producing persistent hypertension by continuous injections of renin, since results obtained in the past have been contradictory.

of hypertensin formed does not exceed one unit We have more recently found that the best results may be obtained by using not more than 2 cc. of plasma or serum.

Renin must be present in excess in order to produce the complete transformation of hypertensinogen. The amount depends upon the activity of each preparation and on the species from which the hypertensinogen has been obtained Since the presence of large quantities of renin does not interfere with the reaction, it is best to add an excess of renin in amounts not less than 100 units per unit of hypertensinogen to be tested (Taquini, Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1943)

For the assay of human hypertensinogen by the same method, Haynes and Dexter (1943) and Dexter, Haynes and Bridges (1945) have used less renin and a more prolonged period of incubation (20 minutes) on the basis that nonhemolyzed human plasma contains less hypertensinase than beef or dog plasma Sapirstein, Reed and Southward (1944) described a method of assay of hypertensinogen based on its incubation with renin at 0°C at which temperature the renin-hypertensinogen reaction occurs at an appreciable velocity while the reaction between hypertensin and hypertensinase is negligible.

The time of incubation used for the measurement of hypertensinogen must be short in order to avoid the action of hypertensinase which may be present in the hypertensinogen employed When renin is present in sufficient amounts, the hypertensinogen is entirely transformed in 5 to 10 minutes The temperature should be maintained between 37 and 40°C and the pH between 7.5 and 8 in order to obtain the maximum velocity of reaction (Taquini, Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1943)

UNIT OF HYPERTENSINOGEN The amount of hypertensinogen is considered to be proportional to the amount of hypertensin formed One unit of hypertensinogen is that amount which when incubated with an excess of renin, under the conditions described above, gives rise to the formation of one unit of hypertensin

SOURCE OF HYPERTENSINOGEN

Hypertensinogen is found in blood plasma Kohlstaedt, Page and Helmer (1940) reported its presence in red blood cells as well as in

tor and proposed in its stead the term "renin-substrate (alpha-2 globulin)" It should be pointed out that this name is too long and does not improve the nomenclature. Actually it has the inconvenience of emphasizing the enzymatic character of the reaction which as yet has not been definitely established. If renin is really an enzyme, it is possible that it may act upon some other substrate as yet unknown. In such a case, the term renin-substrate would not be specific for the precursor of hypertensin.

We believe that the name hypertensinogen is the most appropriate since it is simple and logical and refers to the most important property of this substance which is that of giving origin to hypertensin

MEASUREMENT OF HYPERTENSINOGEN

The presence of hypertensinogen in a solution can be demonstrated by incubating it with renin and testing for the appearance of hypertensin formed

Page and Helmer (1940b) and Page (1942) measured hypertensinogen (renin-activator) by incubating it with renin and measuring the resultant vasoconstrictor action by perfusing it through the vessels of the rabbit's ear This method has a certain qualitative value but is of little value for quantitative measurements, and as Landis (1944) has recently shown, is unreliable unless a meticulous technique is used.

Leloir, Muñoz, Braun-Menéndez and Fasciolo (1940a) devised a much more precise and specific technique for the determination of hypertensinogen It consisted of incubating serum or plasma with an excess of renin The units of hypertensin formed, which were assumed to be equal to the number of units of hypertensinogen present, were determined by their pressor effect when injected intravenously into an anesthetized dog or cat. In using this method, several factors must be controlled (1) the presence of hypertensinase; (2) the amount of plasma, serum or globulin employed; (3) the amount of renin, (4) the time of incubation; (5) the temperature of incubation, (6) the pH of incubation The presence of hypertensinase is important because it can give faulty results by destroying part of the hypertensin formed In order to avoid this, hypertensinase-free renin must be used Leloir, Muñoz, Braun-Menéndez and Fasciolo (1940a) advocated the use of about 10 cc. of plasma, serum or globulins although as we shall see later it is better if the amount

blood concentration of hypertensinogen until it finally disappeared. According to their data, destruction of hypertensinogen would be permanent were it not for its compensatory formation in the liver, and in the absence of the liver it would disappear The investigations of these authors, although important, were not conclusive, since it

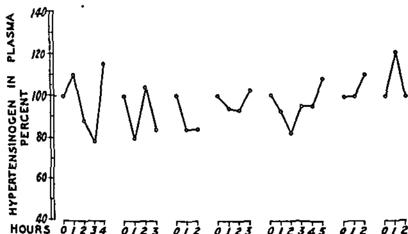


FIGURE 46 VARIATIONS IN THE HYPERTENSINOGEN CONCENTRATION OF PLASMA AFTER ABDOMINAL EVISCERATION

was possible that the disappearance of hypertensinogen was due to a greater production of renin by the kidney as a result of operative shock following hepatectomy.

In order to avoid this difficulty, hypertensinogen was destroyed by injecting renin intravenously or by removing it by plasmaphaeresis in nephrectomized dogs with and without intact livers (Leloir, Muñoz, Taquini, Braun-Menéndez and Fasciolo, 1942) It was demonstrated (1) that hepatectomy did not alter the concentration of hypertensinogen in the plasma of nephrectomized dogs (figure 46), (2) that if nephrectomized and hepatectomized or totally eviscerated animals were given a large amount of renin, the hypertensinogen *disappeared rapidly from the blood and did not regenerate* (figures 47 and 48), and (3) that in nephrectomized or eviscerated

plasma, but this has not been confirmed by us. As we shall see later, red blood cells contain a large amount of an enzyme (hypertensinase) which destroys hypertensin rapidly. This seriously interferes with the measurement of hypertensinogen in red cells since even if hypertensin were formed, it would be destroyed almost immediately. It is therefore extremely difficult to demonstrate the presence of hypertensinogen in red cells and from evidence at hand, its presence in red cells seems unlikely. Unsuccessful attempts have been made to obtain hypertensinogen from such other organs as the liver, spleen, thymus, testicles, lungs, heart, and skeletal muscles. Neither has it been found in milk, hemoglobin, serum albumin and vegetable proteins (Muñoz, Braun-Menéndez, Fasciolo and Leloir, 1940). It is concluded that the only known source of hypertensinogen is blood plasma, although it has been reported to be present in lymph by Friedman, Marx and Lindner (1943) from which it presumably was derived from plasma This has been confirmed by Haynes (Personal communication).

PREPARATION OF HYPERTENSINOGEN

Hypertensinogen may be prepared by precipitating serum with ammonium sulphate (Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1940a). By this procedure, Schales, Holden and Schales (1943) found that most of the hypertensinogen was precipitated between 0 30 and 0 41 saturation at a pH of 6 8. Saturated sodium chloride at pH 5 and 2 M potassium phosphate have also been used to precipitate hypertensinogen (Page and Helmer, 1940). Croxatto and Croxatto (1940) suggested a slight modification of this latter procedure in order to separate hypertensinogen from the enzyme hypertensinase which destroys hypertensin Nonhemolyzed serum was precipitated with 3 [illegible] and hyper- [illegible] phosphate precipitated the hypertensinogen and left the hypertensinase in the filtrate.

ORIGIN OF HYPERTENSINOGEN

Page, McSwain, Knapp and Andrus (1941) were the first to point out that hypertensinogen is formed in the liver. They showed experimentally that removal of this organ or its damage by carbon tetrachloride and ethyl alcohol led to a progressive diminution in the

sinogen free from hypertensinase, since the latter is destroyed at pH 3.9 at 25°C for 30 minutes (see Appendix). According to Dexter, Haynes and Bridges (1945), human hypertensinogen is more labile and is mostly destroyed by this procedure. In order to destroy hyper-

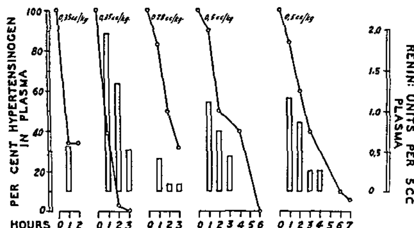


FIGURE 48 VARIATIONS IN THE CONCENTRATIONS OF HYPERTENSINOGEN AND RENIN IN PLASMA

Hepatectomized and nephrectomized dogs were injected with renin Continuous line, hypertensinogen concentration; columns, renin concentration Observe the decrease in hypertensinogen concentration and the lack of its regeneration (After Leloir, Muñoz, Taquini, Braun-Menéndez and Fasciolo, Rev argent de cardiol, 1942, *9*, 269)

tensinase in human plasma without significantly affecting the hypertensinogen content, they added 300 gm. of solid sodium chloride per liter of plasma, stirred until it was dissolved, added toluol as a preservative, lowered the pH to 4 0, and the creamy solution was kept at 37°C. for 4 hours. The pH was then raised to about 6, and the solution dialyzed against water at 5°C until essentially chloride-free Cohn, Oncley, Strong, Hughes, and Armstrong (1944) found that hypertensinogen in human plasma was concentrated in their fraction IV containing predominantly alpha globulin. From the electrophoretic studies of Plentl, Page and Davis (1943), hypertensinogen appears to be an alpha-2 globulin It is stable for months after lyophilization when stored in the ice-box (Dexter, unpublished)

The most important characteristic of hypertensinogen from the

Studies on the biologic specificity of the renin-hypertensinogen reaction, confirmed and amplified in other species,[1] are discussed in detail in Chapter IV.

In addition to an absolute specificity as indicated by a complete absence of reaction between hypertensinogen and renin, a relative specificity has been encountered in several species as indicated by a slowness of reaction Thus, for example, it has been observed that human renin apparently acts more easily on bovine and horse hypertensinogen than on that of the dog (Muñoz, Taquini, Braun-Menéndez, Fasciolo and Leloir, 1943).

No reason has been found to explain the biologic specificity of the hypertensinogen-renin reaction Corcoran, Helmer and Page (1942) believed that this specificity depended more on the hypertensinogen than on the renin They based their opinion on the fact that human renin showed an equal action on the plasma of different mammals, including man, monkey and baboon while the plasma of these primates did not produce hypertensin when incubated with hog, sheep, rabbit, dog or cat renin According to these authors, this would indicate that hypertensinogen rather than renin determines the specificity of the reaction Although the conclusions of these authors bespeak a greater specificity for hypertensinogen, specificity of the renin has in no way been excluded, since if the renins were not different they would behave in the same way on the hypertensinogen of other species

CONCENTRATION IN THE BLOOD

By the methods discussed above, fairly conclusive information has been obtained in regard to the amount of hypertensinogen contained in human plasma and in animals commonly used in experimentation

In man, Haynes and Dexter (1943, 1945) found 2 to 5 cat units per cubic centimeter of plasma which are equivalent to 0 5 and 1 25 dog units Our findings based on a large number of normal subjects are similar, values ranging between 0 5 and 0 7 unit per cc. of fresh plasma (Taquini, Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1943) We believe that it is important for the plasma to be

[1] Eichelberger, Leiter and Geiling 1940, Turnoff and Rowntree, 1941, Schales, Hoobler and Haynes, 1941, Friedman and Kaplan, 1942, Corcoran, Helmer, and Page, 1942

biologic point of view is its specificity. It is acted upon specifically by renin. Braun-Menéndez, Fasciolo, Leloir and Muñoz (1940a) were unable to show that when it was incubated with such enzymes as pepsin, trypsin, or papain, hypertensin was formed. Croxatto and Croxatto (1942a), however, observed that by incubating pepsin with hypertensinogen a substance (pepsitensin) with properties similar to those of hypertensin was formed These findings were later confirmed by us and several other investigators (see Chapter XI) Hyper-

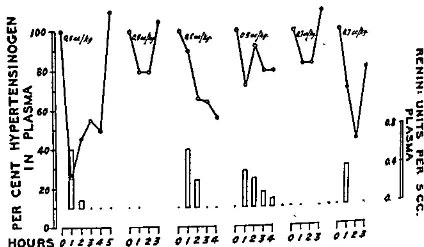


FIGURE 49 VARIATIONS IN THE CONCENTRATIONS OF HYPERTENSINOGEN AND RENIN IN PLASMA

Renin was injected into dogs with complete abdominal evisceration except for the liver which remained *in situ* and was irrigated by the hepatic artery Continuous line, hypertensinogen concentration, columns, renin concentration Observe the decrease in hypertensinogen concentration after the renin injection and the signs of hypertensinogen regeneration (After Leloir, Muñoz, Taquini, Braun-Menendez and Fasciolo, Rev argent de cardiol, 1942, 9, 269)

tensinogen possesses a fairly pronounced zoological specificity. Fasciolo, Leloir, Muñoz and Braun-Menéndez (1940a) showed that pig renin acted *in vitro* on the hypertensinogen of horse, beef, hog and dog, but not on the hypertensinogen of man Human hypertensinogen, however, was acted on by human renin. Battro, Braun-Menéndez, Lanari and Leloir (1940) extended these studies by *in vivo* experimentation and observed that whereas hog renin produced no pressor action in man, human renin had a hypertensive effect.

Menéndez and Fasciolo (1940a) studied the variations of hypertensinogen after nephrectomy and observed a definite increase 48 hours after bilateral nephrectomy This was confirmed by Page and Helmer (1940b) In accord with these studies were the indirect results of Houssay and Dexter (1942) who observed that the pressor response to the intravenous injection of renin was greater in nephrectomized than in normal dogs.

Kohlstaedt, Page and Helmer (1940) claimed to have found an increase of hypertensinogen in hypertensive dogs The results obtained by these investigators may be attributed to the use of an inadequate technique or to the possible presence of renal insufficiency in the animals We, ourselves, have found no change whatsoever in the concentration of hypertensinogen in dogs chronically hypertensive without renal insufficiency An increase has been observed only in those animals with impairment of the excretory capacity of the kidney

Kohlstaedt, Page and Helmer (1940) found no appreciable changes in hypertensinogen after hypophysectomy This was confirmed by Houssay and Dexter (1942)

Houssay and Dexter (1942) found that in some adrenalectomized dogs the response to the injection of renin was reduced and was associated with a fall in the concentration of hypertensinogen of plasma Lewis and Goldblatt (1942) noted a definite diminution and finally an almost complete disappearance of hypertensinogen in the systemic blood in untreated adrenalectomized dogs A return to normal levels occurred following adequate treatment with adrenal cortical hormones or desoxycorticosterone acetate. A fall in the concentration of hypertensinogen is therefore associated with adrenalectomy Before ascribing a direct relationship of this gland to the production of hypertensinogen, it is necessary to exclude the rôle of shock which occurs following adrenalectomy

It has been shown that shock is capable of producing a definite reduction in the amount of hypertensinogen in the blood (Sapirstein, Ogden and Southard, 1941, Huidobro and Braun-Menéndez, 1942; Dexter, Frank, Haynes and Altschule, 1943, Collins and Hamilton, 1944) This diminution is attributable to the liberation of renin into the *circulating blood with the resultant transformation of hypertensinogen* to hypertensin, since it is prevented by previous bilateral nephrectomy (Huidobro and Braun-Menéndez, 1942; Collins and

fresh because apparently
when the plasma is old an

The concentration of demonstrable hypertensinogen in dog plasma is somewhat less, varying between 0.25 and 0.3 unit per cc (Taquini, Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1943). In the rat the amount of hypertensinogen is intermediate between that observed in dogs and man, ranging between 0.30 and 0.40 unit per cc. (Gaudino, 1944). Similar amounts are found in horse and bovine plasma (Taquini, Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1943). We believe that the amount of hypertensinogen contained in plasma of different species under normal conditions is fairly constant The variations observed in some measurements, such as in the wide ranges obtained by Haynes and Dexter, are in our judgment due to such technical difficulties as quantity and activity of the renin, time elapsing since the blood was withdrawn, presence or absence of coagulation, and so forth, the importance of which are still not entirely clear.

Under normal conditions, the same amount of hypertensinogen is found in arterial as in venous blood (Leloir, Muñoz, Braun-Menéndez, and Fasciolo, 1940a).

VARIATIONS UNDER DIFFERENT CONDITIONS. Haynes and Dexter (1943, 1945) reported a normal concentration of hypertensinogen in the plasma of patients with various diseases such as colitis, leukemia, Addison's disease, obesity, Hodgkin's disease, hypertension, and so forth Page (1940d) reported an increase in the concentration of hypertensinogen in some hypertensive subjects These results can not be seriously considered however because the methods employed were unreliable. Using a more precise method, Haynes and Dexter (1943, 1945) found normal values for hypertensinogen in hypertensive subjects We have also found no variation from the normal in hypertensives without renal insufficiency. In cases with renal insufficiency, we have observed a definite increase which is in agreement with the findings of Haynes and Dexter. In man, a decrease in the concentration of hypertensinogen has been demonstrated only in some cases of liver insufficiency (Haynes and Dexter, 1943, 1945).

The concentration of hypertensinogen in serum has been studied under various experimental conditions. Leloir, Muñoz, Braun-

Menéndez and Fasciolo (1940a) studied the variations of hypertensinogen after nephrectomy and observed a definite increase 48 hours after bilateral nephrectomy. This was confirmed by Page and Helmer (1940b) In accord with these studies were the indirect results of Houssay and Dexter (1942) who observed that the pressor response to the intravenous injection of renin was greater in nephrectomized than in normal dogs

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Hamilton, 1942, 1943, 1944; Dexter, Frank, Haynes and Altschule, 1943).

The rôle of the adrenals in regard to hypertensinogen must therefore be determined either in chronic experiments or in those in which adrenalectomy and nephrectomy are performed simultaneously Gaudino (1944) has carried out such experiments in rats, observing that adrenalectomy was followed by a progressive fall in the amount of hypertensinogen in the plasma until practically none could be

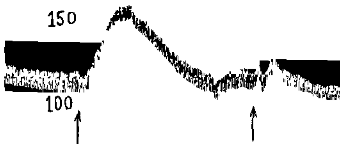


FIGURE 50 DISAPPEARANCE OF HYPERTENSINOGEN FROM PLASMA BY THE INJECTION OF RENIN

Hypertensinogen in the blood of a ten kgm. dog before (first arrow) and after (second arrow) injection [illegible] of serum incubated ten minutes [illegible] *by injection of alcoholi*[illegible] Hg (After Muñoz, Brau[illegible] *200*, 608)

detected at the end of two weeks. If at this time the rats were nephrectomized, the concentration of hypertensinogen increased to a level similar to that observed in nephrectomized dogs that were previously normal It would appear, therefore, that while the adrenals play an indirect rôle in the production of hypertensinogen, they are necessary for its maintenance.

Variations in the concentration of hypertensinogen in different conditions are in most cases explainable by the presence of renin produced by the kidney in the circulating blood. It has been shown experimentally that hypertensinogen becomes diminished or may even disappear as a result of the repeated intravenous injection of renin (figure 50). Since hypertensinogen increases after nephrectomy, it seems possible that there is normally a production of renin capable

of transforming a certain amount of hypertensinogen contained in the plasma to hypertensin.

Hypertensinogen is the substance on which renin acts to produce hypertensin. Up to this time, hypertensinogen has been found only in plasma where it is a component of the alpha-globulin fraction. Hypertensinogen in plasma may be measured by incubating it with an excess of renin and then measuring the amount of hypertensin formed. One unit of hypertensinogen is that amount which gives rise to one unit of hypertensin The normal amount contained in one cc of plasma is approximately 0 75 unit in man, 0 45 in rats, and 0 35 in dogs

Hypertensinogen is formed in the liver. The pituitary is apparently not concerned in its production, while the adrenal appears to play a certain rôle Human hypertensinogen has been found to be increased only in some cases of hypertension with renal insufficiency and to be decreased in liver insufficiency Experimentally, it increases after nephrectomy and in hypertension with renal insufficiency It becomes reduced after injecting renin Shock and hepatectomy in animals with intact kidneys produce a pronounced fall of hypertensinogen due to the liberation of renin Previous nephrectomy prevents its decrease under these circumstances Following adrenalectomy, hypertensinogen becomes reduced, possibly due to the liberation of renin produced by shock or to some mechanism as yet undetermined

CHAPTER VI

HYPERTENSIN

Hypertensin is the product of interaction of renin and hypertensinogen. This same substance was called angiotonin by Page and Helmer (1940a) who claimed to have obtained crystalline derivatives in the form of picrates and oxalates. These studies have not been confirmed. Furthermore, these authors have not described the melting point, elemental composition, relation between weight of the substance and pressor activity, and so forth. In our opinion, therefore, its isolation in pure form must be accepted with reservations.

IDENTIFICATION OF HYPERTENSIN

The identification of hypertensin depends upon biologic methods since no specific chemical reaction has been developed. This is not surprising when one takes into account the difficulties involved in the isolation and characterization of substances which, like hypertensin, are found in dilute and impure solutions, and the structure of which is presumably of a polypeptide nature. Despite innumerable studies on pitressin and insulin, no specific chemical reactions have been found, and their recognition and standardization depend entirely upon biologic methods.

Hypertensin may be differentiated from other vasoconstrictor substances by various biologic and chemical properties. Pitressin, which is similar in solubility, is less resistant to heating with acid, produces a slower and longer rise of blood pressure, and causes tachyphylaxis. Pepsitensin (see Chapter XI) can be differentiated only by its behavior with regard to the hypertensinase of red blood cells which does not destroy it while it does destroy hypertensin (Braun-Menéndez, Fasciolo, Leloir, Muñoz and Taquini, 1943). Adrenalin and other sympathomimetic amines can easily be distinguished from hypertensin since the action of hypertensin is not inverted by Fourneau 933 or by ergotamine. Cocaine which inhibits the pressor action of tyramine does not appreciably alter that of hypertensin. Unlike hypertensin, tyramine has no vasoconstrictor action on the Lawen-Trendelenburg preparation of the toad

ASSAY OF HYPERTENSIN

Of the methods at our disposal at this time, the best consists in measuring the pressor effect of hypertensin on the dog and cat. The recording of its vasoconstrictor action, whether in the extremities of the toad or in the rabbit's ear, is perhaps more sensitive but less specific and quantitative. It is therefore much less reliable.

The rise of blood pressure produced in the dog by an unknown solution of hypertensin is compared with that caused by a solution

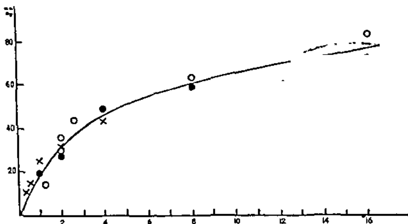


FIGURE 51 INCREASES IN BLOOD PRESSURE PRODUCED BY DIFFERENT AMOUNTS OF HYPERTENSIN

Abscissas Units of hypertensin Ordinates Rise of blood pressure in mm Hg (After Braun Menéndez, Fasciolo, Leloir and Muñoz, *J Physiol*, 1940, *98*, 283)

of known potency In this way, errors arising from varying sensitivities of different animals are diminished For the details of the method, see Appendix

Braun-Menéndez, Fasciolo, Leloir and Muñoz (1940a, b) studied the relation between the amount of hypertensin injected (figure 51) and its pressor action They concluded that within certain limits. the following formula could be applied: $u = \left(\frac{d}{t}\right)^2$ in which *u* represented units of hypertensin in the unknown sample, *d* the rise in mm Hg of blood pressure produced by the injection of the unknown sample, and *t* the rise produced by the injection of one unit of hypertensin Braun-Menéndez, Fasciolo, Leloir and Muñoz (1940a)

defined the unit of hypertensin as the amount which produced a rise of 20 to 30 mm. Hg in the carotid pressure of an average chloralosed dog weighing 10 kgm. It is readily appreciated that this method is applicable only to those solutions which contain no other substances which affect blood pressure.

Some authors have used other substances for comparing the pressor action. Edman, Euler, Jorpes and Sjostrand (1942) employed tyramine phosphate. It is less reliable, however, to use a substance other than hypertensin since the sensitivity of the animal for each substance may vary from one moment to another and from one animal to the next

PREPARATION OF HYPERTENSIN

Hypertensin may be prepared (see Appendix) by incubating given quantities of renin and hypertensinogen under conditions which are optimal for the reaction The pH should be between 7 and 8, and the temperature between 37 and 40°C The proteins may then be removed by heat or by precipitation with alcohol or acetone, and the extract may be suitably concentrated (Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1940a; Page and Helmer, 1940a). Dexter, Haynes and Bridges (1945) described a method of preparation consisting of incubating dialyzed renin and hypertensinogen, recovering the ultrafiltrate, and concentrating Sapirstein, Reed, and Southard (1944), after incubating renin and hypertensinogen at low temperatures, removed the proteins with trichloracetic acid and removed the latter from the filtrate by boiling.

Although several procedures have been devised for the purification of solutions of hypertensin, little advance has been made in the elimination of impurities A second precipitation with alcohol removes salt and some of the inactive material. It can be precipitated with ether from solutions in alcohol or glacial acetic acid It may be separated from aqueous solutions by saturation with ammonium sulphate. Edman, Euler, Jorpes and Sjostrand (1942) made an unsuccessful attempt to purify it by electrophoresis. All investigators who have tried to purify hypertensin report large losses in the various steps of purification (For details of preparation, see Appendix.)

CHEMICAL PROPERTIES

Since the chemical properties of hypertensin have been studied on

extremely impure solutions, it is unwise to place much value on many of the reactions described.

SOLUBILITY. Hypertensin is extremely soluble in water, glacial acetic acid, phenol and ethylene glycol, partially soluble in 96 per cent alcohol and acetone, insoluble in ether, chloroform, petroleum ether, and amyl and butyl alcohol (Muñoz, Braun-Menéndez, Fasciolo and Leloir, 1940, Page and Helmer, 1940a) It can be separated from aqueous solutions by saturation with ammonium sulphate (Muñoz, Braun-Menéndez, Fasciolo and Leloir, 1940, Edman, Euler, Jorpes and Sjostrand, 1942). From dilute aqueous solutions, it is not precipitated with trichloracetic acid according to Page and Helmer (1940a), or with picric acid or silver flavianate or nitrate in acid or alkaline medium It is precipitated with phosphotungstic acid and with mercury salts if the solution is sufficiently concentrated

STABILITY. It is very resistant to heating At neutrality it is stable for more than seven hours at 100°C In a solution of 1 N hydrochloric acid it is stable for two hours, being destroyed after three hours In alkaline solution, it loses its activity in ten minutes at 100°C in 0 15 N sodium hydroxide (Muñoz, Braun-Menéndez, Fasciolo and Leloir, 1940, Page and Helmer, 1940a) It loses its activity by benzoylation by the Schotten Baumann method (Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1940a) and can be recovered by hydrolysis (unpublished)

By incubation with pepsin (figure 52), trypsin, or hypertensinase, it loses its activity The same occurs by bacterial action (Muñoz, Braun-Menéndez, Fasciolo and Leloir, 1940) Croxatto and Croxatto (1941b, c, d) reported its inactivation by incubation with crystalline pepsin or trypsin, or with impure extracts rich in phenol- and amine-oxidase (Chapter VII) Plentl and Page (1944a) showed it to be destroyed by incubation with crystalline carboxypeptidase, chymotrypsin, trypsin and pepsin

It is preserved indefinitely in the dry state, or in neutral or acid aqueous solution at a low temperature. It passes through cellophane on dialysis Preliminary attempts (unpublished) to determine the molecular weight by diffusion have yielded figures varying between 400 and 1,000. According to Edman, Euler, Jorpes and Sjostrand

due which might be part of (4) and if not part of (4) would have to be terminal with its carboxyl group in peptide linkage. They also concluded that the simplest compound meeting these requirements was tyrosyl-arginyl-glutamyl-phenylalanine.

Hypertensin may be considered to be a polypeptide because of its inactivation by proteolytic enzymes (pepsin, trypsin, chymotrypsin, carboxypeptidase), because of its isoelectric point between pH 6.3 and 6.5, and because of its general characteristics of solubility and precipitability which are similar to those of pitressin. This opinion has been sustained by Braun-Menéndez, Fasciolo, Leloir and Muñoz (1940a), Croxatto and Croxatto (1941a), Cruz Coke (1945), and Edman, Euler, Jorpes and Sjostrand (1942). The only contrary evidence is that of Page and Helmer (1940a) who reported that the biuret reaction was negative. This may possibly have been due to the use of too dilute solutions. Further evidence in favor of the polypeptide nature of hypertensin is that it is formed by the splitting off of a part of the protein molecule (hypertensinogen) by a reaction which is probably hydrolytic. Furthermore, it is dialyzable and appears to have a molecular weight between 400 and 1,000.

PHARMACOLOGIC ACTION

The pharmacologic actions of hypertensin are in most respects identical with those of renin, since the action of the latter is due to the formation of hypertensin. In this chapter, therefore, many statements may appear to be a simple repetition of what has already been said concerning the pharmacologic reactions of renin, but actually they refer to studies made separately in the course of systematic investigation.

PRESSOR ACTION. *Routes of Administration*.—The only satisfactory routes of administration for the production of hypertension are by vein or artery. No rises of pressure have been obtained by the administration of hypertensin subcutaneously, intramuscularly, or intraperitoneally, possibly due to the use of insufficient doses. Dexter and Haynes (personal communication) have injected as much as 100 dog units intramuscularly into a cat without obtaining a pressor response.

Burlingame, Long and Ogden (1942) injected renin and hypertensin into pregnant rats and into fetuses, observing that the fetuses

were much less responsive than the mothers. When injected into the mother, no hypertension was produced in the fetus In many cases hypotension actually developed These authors did not believe that it was the molecular size of hypertensin which impeded its passage across the placenta since adrenalin, with its small molecular size and ready diffusibility, likewise produced no hypertension in the fetus It seems possible that the cause of the diminution of fetal blood pressure was due to rhythmical contractions of the uterus from injection of the substances studied

Latent Period.—The pressor action of hypertensin takes place within a few seconds depending upon the rapidity with which it becomes distributed in the vascular system Hypertensin injected into the descending aorta produces hypertension within 6 to 8 seconds, in the jugular vein in 15 seconds, in the saphenous vein in 18 seconds, and in the carotid artery in 35 seconds (Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1940b).

Form of the Curve.—The rise of systolic and diastolic pressure reaches a maximum within a few seconds (figure 52) Immediately afterwards the curve falls, and the pressure returns to normal within 2 to 8 minutes according to the amount injected The descending limb of the curve reaches the initial level of blood pressure without a secondary fall as occurs after an injection of adrenalin The greatest rises of pressure obtained have been 90 to 100 mm Hg which were produced by 15 to 20 units of hypertensin in dogs weighing 10 kgm.

Response to Repeated Injections.—As mentioned in Chapter IV, many substances produce a diminishing pressor response on repeated injection (renin, pitressin, veritol, ephedrine, and so forth) This phenomenon is known as tachyphylaxis Page and Helmer (1940b) reported that they had observed tachyphylaxis to hypertensin which has not been confirmed As long as the experimental conditions remain constant (level of blood pressure, degree of anesthesia, artificial respiration, temperature of the animal, and so forth), the injection of a given amount of hypertensin produces the same response each time that it is repeated, even though the interval between injections is short We have found repeatedly that 15 to 20 injections in two or three hours produce the same response each time.

Tachyphylaxis exists only in the toad and serpent (Bean, 1942a, b). According to Bean, this is probably due to the fact that in these animals the destruction of hypertensin takes place very slowly be-

cause hypertensinase has a slow action at 15 to 18°C. For the reasons discussed (Chapter IV) the slow destruction of hypertensin would explain the appearance of tachyphylaxis in these animals (figure 53) (Bean, 1942a).

Continuous Injection.—If hypertensin is injected intravenously into an animal slowly and continuously for 30 minutes, a rise of



FIGURE 53 PROLONGED PRESSOR ACTION OF HYPERTENSIN IN THE TOAD

blood pressure is produced and is maintained throughout the infusion of hypertensin (figure 54) (Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1940a).

Conditions which Modify the Reaction to Hypertensin.—The pressor action of hypertensin is produced even after section of the vagi and splanchnics, after removal of the carotid sinuses, and after

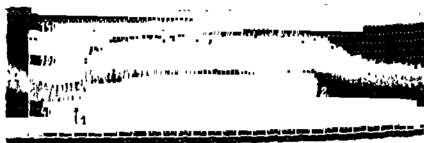


FIGURE 54 CONTINUOUS INTRAVENOUS INJECTION OF HYPERTENSIN

Dog, 6.5 kgm., chloralosed. Double vagotomy. Artificial respiration. Femoral blood pressure in mm. Hg. Time in minutes. (1) intravenous injection of hypertensin is started at a rate of one unit/min., (2) end of injection (After Braun-Menéndez, Fasciolo, Leloir and Muñoz, *J. Physiol.*, *1940, 98, 283*)

destruction of the medulla and of the spinal cord. In the latter instance, the pressor action is somewhat weaker. Gregory, Levine and Lindley (1944) observed no diminution of its pressor action in normal and hypertensive patients under spinal anesthesia or in dogs

after bilateral vagotomy or section of the low cervical cord Removal of the kidneys, liver or all the abdominal viscera does not inhibit its action (figure 55). These observations indicate that its action is not mediated by the nervous system, and that the presence of the ab-

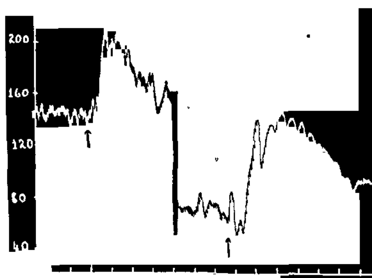


FIGURE 55 ACTION OF HYPERTENSIN ON AN EVISCERATED DOG

Femoral blood pressure in mm Hg of an 18 kgm chloralosed dog Intravenous injection of three units of hypertensin before (first arrow) and after (second arrow) evisceration. Time in minutes (After Braun Menéndez, Fasciolo, Leloir and Muñoz, Rev Soc argent de biol, 1940, *16*, 398)

dominal viscera is not necessary (Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1940a, b)

Animals in shock react less or not at all to hypertensin (Page, 1943a; Middleton, 1944) The same is true of animals which have previously received large doses of renin.

In hypertensive animals, the sensitivity to hypertensin is not appreciably altered (see Chapter II) Nephrectomy performed 24 to 48 hours before appears to produce a greater sensitivity (Page and Helmer, 1940b; Houssay and Dexter, 1942) (see Chapter IX) It is natural that after such a serious operation involving varying degrees of shock, infection, uremia, and so forth, the responses observed vary from one animal to the next.

Removal of the adrenals or of the pituitary does not appreciably modify the sensitivity to hypertensin unless shock supervenes (see Chapter X).

Action of Drugs—The pressor action of hypertensin is considerably potentiated by the previous injection of veritol (50 to 60 mgm per kgm), ephetonine (0.1 mgm. per kgm.) (figure 56a), or tyramine (figure 56b). The synergistic action of ephetonine is extremely prolonged, lasting about 40 minutes. Cocaine (10 mgm. per kgm.) and

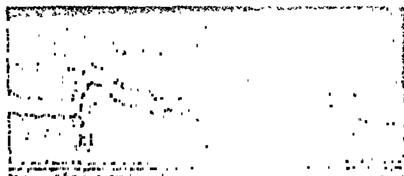


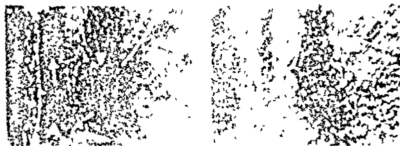
FIGURE 56A. POTENTIATING ACTION OF EPHETONINE ON THE ACTION OF HYPERTENSIN

Chloralosed dog weighing five kgm Carotid pressure in mm. Hg Time in minutes H, 0.5 cc hypertensin, E, 1 mgm ephetonine (After Braun Menéndez, Fasciolo, Leloir and Muñoz, Rev. Soc argent de biol, 1940, *16*, 398).

pyrogallol (20 mgm. per kgm) have less effect. Pitressin (0.5 to 1 unit) reduces somewhat the pressor action of hypertensin. Renin diminishes or abolishes it The injection of Fourneau 933 (10 mgm. per kgm.) does not alter the action of hypertensin, although it is well known that this drug inverts the action of sympathomimetic substances such as adrenalin. Atropine (1 mgm. per kgm.) and adrenalin (0.5 gamma per kgm.) do not alter the action of hypertensin (Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1939, 1940b; Page and Helmer, 1940a, b) Mardones and Lorraine (1944) observed that cysteine did not potentiate the action of hypertensin on the blood pressure of decerebrate cats.

VASOCONSTRICTOR ACTION. We have seen that the pressor action of hypertensin exists despite section of such nerves as the vagi and splanchnics, and despite destruction of the central nervous system. Its action therefore is peripheral. The vasoconstrictor action of hypertensin has been studied by different methods, including the





larger doses, and the capillaries did not contract. Tyramine and methylguanidine had similar actions. Adrenalin and pitressin had a more intense and prolonged action on arterioles and venules These substances, however, did not cause the capillaries to contract In the intact animal, the action of renin on vessels was the same as that of hypertensin except that it was slower.

According to Page and Helmer (1940b), the injection of hypertensin in Ringer's solution produced intense vasoconstriction when perfused through the rabbit's ear. The second injection had less effect, and the third none. The addition of normal blood or of certain extracts of blood to the perfusing fluid restored the vasoconstrictor action of hypertensin The substance responsible for this effect was called angiotonin-activator or co-substance The authors concluded that angiotonin-activator was necessary for the action of hypertensin It is of interest to recall the studies of Morton and Tainter (1940) in this regard When the lower extremities of the cat were perfused with Locke's solution, the vasoconstrictor action of tyramine and ephedrine became diminished or even absent. The action reappeared if the leg was perfused with defibrinated blood or heparinized plasma, or by adding adrenalin to Locke's solution. From these observations, Morton and Tainter suggested that the vasoconstrictor action of amines in the group of tyramine and ephedrine was due at least in part to blocking of the local mechanisms which inactivate adrenalin It is probable, however, that the state of the vessels and therefore their reactivity, play some rôle since the addition of 0 5 per cent gelatin to Locke's solution was sufficient to increase the activity of these drugs considerably

In the toad the phenomenon observed by Page and Helmer does not occur (Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1940b) In the Lawen-Trendelenburg preparation perfused with Ringer's solution, the action of hypertensin is consistently vasoconstrictor, although the injections are repeated many times. In dog and horse plasma, we have not encountered an activator of the vasoconstrictor action of hypertensin For these reasons, we consider that the existence of angiotonin-activator is extremely doubtful.

ACTION ON HEART. In general, pressor and vasoconstrictor substances are considered to be the same. Certain substances, however, may produce an increase of pressure without vasoconstriction, either

by producing an increase in the amount of circulating blood or an increase in the minute volume output of the heart while vasoconstriction may occur without an increase of blood pressure as occurs at times with pitressin.

The pressor effect of hypertensin is due not only to the vasoconstriction which it produces, but also to its effect upon the heart. The experiments of Hill and Andrus (1941), Lorber and Visscher (1941) and Lorber (1942) have shown that hypertensin increases the amplitude and force of ventricular systole, the minute volume output, and the consumption of oxygen as well as the work performed by the heart and its efficiency It produces vasoconstriction of the coronaries, while the pulse rate and the electrocardiogram are not changed. Middleton and Wiggers (1944), however, have reported that small doses of hypertensin do not alter significantly the systolic discharge but, because of a concomitant slowing, the cardiac output is slightly reduced With doses producing a rise of 30 mm Hg or more, they found a variable reduction of systolic discharge which, together with a slowing of heart rate, resulted in a considerable reduction of cardiac output Haney, Lindgren, Karstens and Youmans (1945) found that hypertensin did not produce bradycardia in the denervated heart of the dog

ACTION ON KIDNEY Corcoran and Page (1940b, 1941b) and Corcoran, Kohlstaedt and Page (1941a) studied the effect of hypertensin on the kidney using the indirect methods of phenol red, inulin and diodrast clearance in man and dogs Renal blood flow and glomerular filtration can be measured by these methods, and the relation between these two permits the determination of the filtration fraction (see Chapter II). The filtration fraction bears a relation to the pressure in the glomerular capillaries (filtration pressure) which in turn is conditioned by the state of constriction of the efferent glomerular arterioles The results obtained by these authors were the same in both species Hypertensin produced diminution of renal blood flow and increase of the filtration fraction, which was attributable to an increase of intraglomerular pressure and therefore to a constriction of the efferent arterioles of the glomeruli

Corcoran and Page (1940a) also investigated unilaterally nephrectomized dogs with the other kidney explanted so that samples of blood could be taken from the renal vein From the concentration

of a given substance in the arterial blood, renal venous blood, and from the amount eliminated in the urine, the amount of blood passing through the kidney in a given time could be calculated. By determining the extraction ratio of phenol red and inulin, they showed that the infusion of hypertensin into unanesthetized dogs

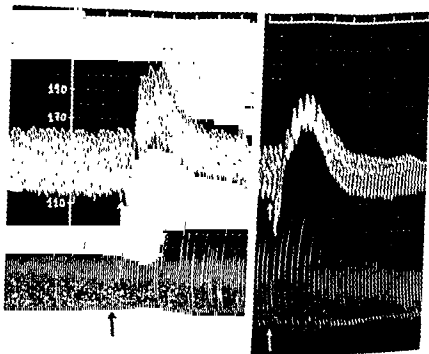


FIGURE 58 ACTION OF HYPERTENSIN ON BLOOD PRESSURE AND RESPIRATION

Action of hypertensin on the blood pressure (upper curve) and respiratory movements (lower curve) of a dog weighing thirteen kgm under chloralose anesthesia before (left) and after (right) bilateral vagotomy. Time in minutes Blood pressure in mm Hg. At the arrows, five units of hypertensin were injected intravenously (After Braun-Menéndez, Fasciolo, Leloir and Muñoz, Rev. Soc argent. de biol, 1940, *16*, 398)

produced a rise of blood pressure, diminution of renal blood flow, and increase of extraction of inulin by the kidney. These results were similar to those produced by renin, but with hypertensin the effects were manifest earlier and disappeared more rapidly when the injection was stopped.

Hypertensin therefore produces constriction of the efferent arterioles of the glomerulus as has also been observed by Smith.

Goldring, Chasis and Ranges (1938) in human beings with essential hypertension Herrick, Corcoran and Essex (1941) using the thermostromuhr also found a reduction of renal blood flow. Braun-Menéndez, Fasciolo, Leloir and Muñoz (1940b) observed vasoconstriction by measuring the volume of the kidney.

Wakim, Root and Essex (1941) made microscopic observations on the changes occurring in the kidney of the frog by direct application of hypertensin or by its intravenous injection In both cases, transitory vasoconstriction was produced and glomerular activity stopped for a minute. This was followed by a moderate congestion which lasted some eight minutes. When the drug was injected into the lymphatic sac, the initial cessation of activity was not produced while congestion did occur. No action on the kidney of the frog was observed after the injection of renin.

ACTION ON RESPIRATION. Respiration is little changed by hypertensin. In general, a transient tachypnea is observed followed by a slight prolonged reduction of respiratory rate. Anesthesia does not modify this effect and vagotomy does not prevent it (figure 58) (Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1940a) Wilkins and Duncan (1941) found in man a reduction of the vital capacity

ACTION ON OTHER ORGANS Braun-Menéndez, Fasciolo, Leloir and Muñoz (1940b), using a plethysmograph, showed that the intravenous injection of hypertensin produced a diminution in the volume of the spleen, kidney and intestine (figure 59). Injection of 0 1 to 1 unit of hypertensin into the arteries of the stomach, duodenum, intestine, spleen and kidney produced a marked and lasting vasoconstriction According to Page and Helmer (1940a), it produced an increase in tone of the isolated rabbit intestine without reducing rhythmical movements

Harrison and Ivy (1941) reported that hypertensin produced a contraction of the isolated gall bladder of the guinea pig and of the gall bladder and duodenum of the dog *in situ*.

METABOLIC ACTION Foglia and Moglia (1940) observed an abrupt but transient increase of the plasma potassium which was prevented by a previous injection of Fourneau 933 or by hepatectomy. The blood sugar also increased, although somewhat later than

the rise of potassium, and this effect was also more prolonged. In dogs without the adrenals, the blood sugar was not changed. The hyperglycemia produced by hypertensin is probably indirect and due in part to a small discharge of adrenalin. Indeed, Braun

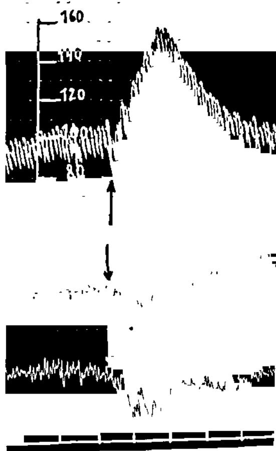


FIGURE 59. ACTION OF HYPERTENSIN ON THE DOG'S INTESTINE "IN SITU"
Action of three units of hypertensin intravenously on blood pressure in mm Hg (upper curve), intestinal motility (middle curve); and volume of the intestine (lower curve). Time in minutes (After Braun-Menéndez, Fasciolo, Leloir and Muñoz, Rev Soc argent de biol, 1940, *16*, 398)

Menéndez, Fasciolo, Leloir and Muñoz (1940b) were able to show with cross-circulation experiments that the injection of hypertensin produced a small discharge of adrenalin (figure 60).



FIGURE 60 DISCHARGE OF ADRENALIN FROM AN INJECTION OF HYPERTENSIN (ANASTOMOSIS BETWEEN THE ADRENAL AND JUGULAR VEINS)

Femoral pressure in mm Hg of dog 1 weighing 15 kgm under chloralose anesthesia, whose jugular vein was anastomosed to the adrenal vein of dog 2 weighing 23 kgm Time in minutes The injection of seven units of hypertensin

ACTION ON SMOOTH MUSCLES Ludueña (1940), who has made the most complete pharmacologic study to date of the action of hypertensin on smooth muscles, concluded that it produced contraction of almost all organs investigated, although the sensitivity of different organs varied. The most sensitive organ found was the rat uterus (figure 61) and rabbit uterus (figure 62), which were responsive to dilutions of 1 unit diluted to 1,250 to 2,000 The small intestine of dog, guinea pig and rabbit, and the uterus of the guinea

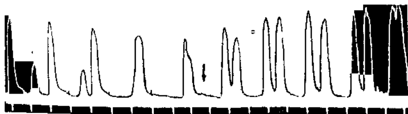


FIGURE 61 ACTION OF HYPERTENSIN ON THE NON PREGNANT RAT UTERUS

At the point indicated by the arrow, hypertensin was added to the bath The resulting concentration was one unit in 1250 cc A progressive increase in the rhythmical contractions is observed Time in minutes (After Ludueña, Rev Soc argent de biol, 1940, *16*, 358)

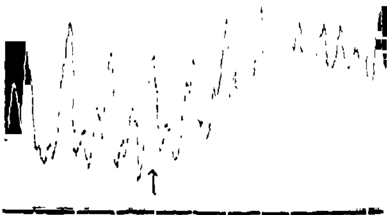


FIGURE 62 ACTION OF HYPERTENSIN ON THE NON-PREGNANT RABBIT UTERUS
At the arrow, hypertensin was added to the bath in a concentration of o
unit in 2000 cc. Time in minutes (After Ludueña, Rev. Soc argent de bio
1940, *16*, 358)

pig were sensitive to dilutions of 1 in 750. The sensitivity of th
dorsal muscle of the leech increased from 1:15 to 1:150 followin
eserinization The gall bladder, retractor penis, ureter, vas deferen

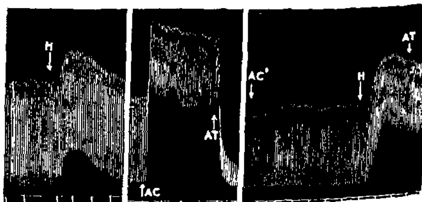


FIGURE 63 ACTION OF HYPERTENSIN ON THE SMALL INTESTINE OF A RABBIT
H, hypertensin one unit in 75 cc.; AC, acetylcholine, 1.18,000,000, AT, atropine
1 60,000, AC', acetylcholine 1 6,000,000, note that atropine sulphate, which
abolishes the motor effect of acetylcholine, does not modify the action of hyper-
tensin Time in minutes (After Ludueña, Rev Soc argent de biol, 1940, *16*,
358).

and bronchi of dogs were sensitive to dilutions between 1 in 60 and 1 in 15.

The action of hypertensin on smooth muscles has certain peculiarities which Ludueña has described. The latent period of action is much longer than that of adrenalin or acetylcholine, both in isolated organs and in organs *in situ* The stimulating effect is characterized by an increase in tone. If the organ has rhythmical contractions, these become reinforced, as in the case of uterus and intestine. In other cases, rhythmical contractions may be produced as in the case of the uterus, intestine, bladder, retractor penis and gall bladder. In some cases, such as the intestine, an initial inhibition may be produced It dilates the pupil, although this action is very weak. It is best seen in the cat anesthetized with nembutal, where miosis is extreme. It produces contraction of the nictitating membrane of the cat, preceded at times by inhibition of the membrane This action is diminished or abolished by Fourneau 933

The analysis of Ludueña of the action of hypertension indicates that it may be classed among the musculotropic drugs since it contracts the uterus of the rat and the intestine of dog, rabbit and guinea pig, which are relaxed by adrenalin and stimulation of the sympathetic nerves It contracts the intestine and pieces of bladder made insensitive to *acetylcholine* by *atropine* (*figure 63*) Its *motor action* parallels neither sympathetic nor parasympathetic nerve action Its action on the uterus differs from that of histamine since the latter contracts the uterus of rabbits and guinea pigs as does hypertensin, but inhibits that of rats.

According to Ludueña, the most sensitive reactor to hypertensin is the vascular system of the dog and the second most active, the rat and rabbit uterus It is well to bear these facts in mind in the evaluation of different methods of assay of hypertensin

ACTION ON MAN The action of hypertensin on man has been studied by Battro, Braun-Menéndez, Lanari and Leloir (1940); Battro, González-Segura and Lanari (1941), Corcoran, Kohlstaedt and Page (1941a), Bradley and Parker (1941) and Wilkins and Duncan (1941) The injection of hypertensin in man produces systolic and diastolic hypertension with the same characteristics as in the experimental animal The action is rapid and varies with the dose (figure 64).

Bradley and Parker (1941) reported an increase of peripheral resistance and of blood pressure and bradycardia with diminution of the minute volume output without modification of the systolic output. Wilkins and Duncan (1941) reported an increase of arterial and venous pressure, bradycardia, marked diminution of the systolic output, increase in cardiac size, prolongation of the circulation time, diminution of blood flow to the extremities as indicated by plethysmographic studies and skin temperature, and little change in spinal fluid pressure With single injections or during continuous injections, untoward symptoms at times occurred, consisting of precordial oppression, palpitation, and nausea and vomiting which disappeared within a few minutes of stopping the injection. Taylor and Page (1943b) observed that hypertensin decreased the systolic discharge and the heart rate, and produced a marked reduction in cardiac output The variations in heart rate which are observed in man are of vagal origin and abolished by atropine (Battro, González-Segura and Lanari, 1941).

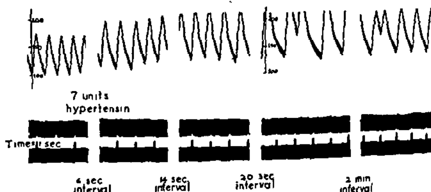


FIGURE 64. ACTION OF HYPERTENSIN ON MAN

Intra-arterial pressure in mm Hg taken with the Hamilton manometer before and after an intravenous injection of seven units of hypertensin (After Battro, *Braun-Menéndez, Lanari and Leloir, Rev. Soc. argent de biol*, 1940, *16*, 376).

CONCERNING THE PHARMACOLOGY OF VARIOUS PRESSOR SUBSTANCES

Hypertensin belongs to that important group of substances which acts on autonomous, glandular or muscular effectors, the main physiologic representatives of which are adrenalin and acetylcholine.

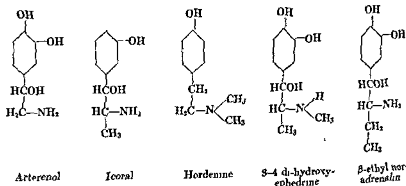
The precise manner in which these drugs act is not entirely clear. It was formerly believed that they acted on the sympathetic and parasympathetic nerve endings of cells With further investigation, however, this concept became untenable The variety of actions of each drug were so great and the effects on different effector organs so contradictory that gradually all attempts at classification which tried to include all the known facts had to be discarded.

Despite these difficulties, Tainter (1932, 1933) proposed a practical classification which, despite certain objections, is useful in pharmacologic analyses of drugs. His procedure was as follows: Adrenalin is injected repeatedly into cats until a constant pressor response of 30 mm. Hg is obtained The substance to be studied is then injected, following which the animal is cocainized by the administration of 15 mgm. of cocaine per kgm subcutaneously Fifteen minutes later, a re-injection of adrenalin produces a pressor response which is twice that before the injection of cocaine since cocaine potentiates the action of adrenalin. Injection of the unknown substance is repeated, and if the response is greater than before cocainization, the drug, behaving like adrenalin, is sympathomimetic If the response is the same as before, the substance acts like barium or pitressin and is considered to be musculotropic If the response is less or absent, it behaves as ephedrine or tyramine and is considered to be pseudo-sympathomimetic Hypertensin behaves as a musculotropic substance. Tainter then injects ergotamine, 1 mgm at a time, until the pressor action of adrenalin becomes inverted, 0 6 to 1 mgm. per kgm. of ergotamine usually suffices The unknown substance is then injected and if hypotension is produced as in the case of adrenalin, it is considered to be sympathomimetic If the response is unchanged, as in the case of barium, it is considered to be musculotropic, and if the action is diminished, it is considered to be pseudo-sympathomimetic. By this second criterion, hypertensin also behaves as a musculotropic substance Before ending the experiment, adrenalin is again injected in order to make sure that the effect of ergotamine still persists Hypertensin can be considered as a musculotropic substance since *its pressor action is not modified by cocaine or ergotamine.*

Conclusions from studies on the properties of drugs must be made with caution since not only are the experimental conditions important, but also the results obtained may not be applicable to animals of other species. Thus, tyramine is sympathomimetic in the cat, has

can also be formed by action of the "cytochrome C, cytochrome oxidase, oxygen" system, which is present in all animal tissues Through its oxidizing and reducing properties, adrenochrome can serve, in artificial systems at least, as a carrier of hydrogen in the oxidation of different metabolites such as lactic and malic acids (Green and Richter, 1937) Adrenochrome has no pharmacologic action

Recently, a phenol oxidase system has been described which may have greater physiologic importance and may explain the transitory action of adrenalin. We refer to the transformation of adrenalin into *adrenoxin*. Bacq and Heirman (1940) found that incubation of dilute solutions of adrenalin or other sympathomimetic substances with extracts of animal or vegetable tissues containing phenol oxidases caused the vasoconstrictor action of adrenalin to disappear. The incubated mixture acquired strong hypotensive properties and an inhibiting effect on the isolated heart of batrachians and on the isolated intestine of rabbits. These investigators attributed these changes in the properties of adrenalin to undetermined phenomena of oxidation. The catalyzers of this reaction were found to be oxidases from vegetables (potatoes and mushrooms), from animals ("tyrosinase" from Tenebrio mollitor), or from organ extracts In the latter instance, the only extracts possessing this catalyzing action came from organs, the activity of which was inhibited by adrenalin, the only exception being the small intestine.



Arterenol *Icoral* Hordenine 3–4 di-hydroxy-ephedrine *β-ethyl nor-adrenalin*

Substances which give rise to adrenoxin are adrenalin, epinine, oxytyramine, tyramine and para-sympathol. Adrenoxin has not been obtained from arterenol, icoral, hordenine, dioxy-ephedrine or beta ethyl-noradrenalin.

Adrenoxin presents a number of peculiarities It is produced, for

example, *only by using dilute solutions of substrate* (10^{-5}, 10^{-6}). *Due* to its instability, its action is manifest only for a short time, varying from one to four hours with different preparations. With shorter or longer incubations, its presence may not be detected. Progesterone inhibits its production It will be remembered that progesterone *reverses the action of adrenalin on the uterus of virgin cats Cyanide* and resorcinol also inhibit its formation

The physiologic significance of adrenoxin has not as yet been established. As its discoverers believe, it may be the cause of the secondary effects of adrenalin or of the effects produced by extremely small doses of adrenalin The slowness of its production *in vitro* does not invalidate its possible physiologic rôle

The similarity of action of these sympathomimetic substances with hypertensin justifies, in our judgment, the review which we have presented Furthermore, the action of these various enzymes may be of value in the study of the problem of hypertension.

Hypertensin is a pressor and vasoconstrictor substance resulting from the interaction of renin and hypertensinogen It is probably a polypeptide of relatively low molecular weight It is dialyzable, thermostable, acid resistant and alkali labile It is destroyed by proteolytic enzymes such as pepsin and trypsin. It is soluble in water and insoluble in organic solvents Its purification is difficult, and its presence can be detected only by its pharmacologic action It may best be assayed by its pressor action in the dog or cat. Injected intravenously into animals, it produces a characteristic rise of blood pressure of short duration This action is not inverted by Fourneau 933 nor modified by cocaine It is potentiated by veritol, tyramine and ephetonine. The unit of hypertensin is defined as that amount which produces the same rise of pressure as is produced by one cc. of our standard solution, which produces an elevation of 20 to 30 mm Hg pressure in the average 10 kgm dog anesthetized with chloralose It has a stimulating action on the heart, and produces vasoconstriction of the efferent arteriole of the glomerulus of the kidney In general, it produces contraction of smooth muscles and may be classified among the drugs having a musculotropic action.

Prolonged hypertension may be obtained by its continuous injection, a blood pressure curve being obtained which is similar to that produced by the intravenous injection of renin

CHAPTER VII

HYPERTENSINASE

In earlier experiments on the formation of hypertensin *in vitro*, it was observed that if the incubation of renin with hypertensinogen were too prolonged, a disappearance of hypertensin would occur (Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1939, Page and Helmer, 1940a) At that time, it was not clear whether this action was due to the renin itself or to the presence of some other substance Later experiments (Leloir, Muñoz, Braun-Menéndez and Fasciolo, 1940a) showed that by using purer preparations of renin and hypertensinogen, the disappearance of hypertensin could be avoided Furthermore, the incubation of hypertensin with impure renin caused hypertensin to disappear. This did not occur with purer preparations of renin.

The disappearance of hypertensin was attributed to the action of an enzyme which was called hypertensinase. Findings which suggest that it behaves as an enzyme are as follows: It is thermolabile, it does not dialyze, it possesses an optimum pH and temperature of reaction Different tissues possess a hypertensinase action At the moment it is not entirely clear whether there are one or many different enzymes; the latter appears more probable. Page and Helmer (1940b) described a substance which they called "angiotonin-inhibitor" which was possibly the same as hypertensinase.

GENERAL PROPERTIES

Hypertensinase is probably a protein. Regardless of whether it is of red cell or renal origin, it is precipitated with ammonium sulphate between 0 3 and 0.6 saturation. It is not precipitated by dialysis against distilled water. In neutral solution, it is inactivated in a few minutes by heating to 60°C. or in 20 minutes at 25°C when the pH is between 3.6 and 3 9 The following substances do not affect its activity: Toluol, chloroform, thymol, potassium cyanide, octyl alcohol, 0 02 M sodium fluoride, pyrogallol, sodium bisulphite. It is likewise unaffected by anaerobiosis (Fasciolo, Leloir, Muñoz and Braun-Menéndez, 1940b). The pH optimum of hypertensinase of red

blood cell origin is between 7 and 8 This was determined by Muñoz, Braun-Menéndez, Fasciolo and Leloir (1940) (see figure 40).

Helmer, Kohlstaedt and Page (1942) observed that the hypertensinase of muscle, liver and intestine had an optimum pH between 7 and 8, and that it was practically inactive at pH 4. For the hypertensinase of kidney, however, the optimum pH was 4 They concluded justifiably that there were two hypertensinases, one which acted at pH 7 to 8, the other at pH 4.

Its activity at different temperatures has been studied by Bean (1942a) in the blood of man, ox, dog and toad (figure 65) At 20°C.

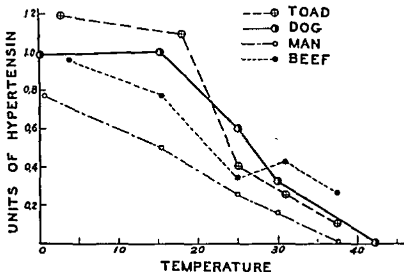


FIGURE 65 ACTIVITY OF RED BLOOD CELL HYPERTENSINASE AT DIFFERENT TEMPERATURES

Hypertensinase activity determined from the amount (units) of hypertensin left in the solution after two hours' incubation at various temperatures with hypertensinase (After Bean, Am J Physiol, 1942, *136*, 731)

the activity was decidedly diminished, and according to Bean this accounted for the occurrence of tachyphylaxis to hypertensin in the toad At 0°C its activity is negligible according to Bean (1942a) and Sapirstein, Reed, and Southard (1944) Plentl and Page (1944) in studying the action of hypertensinase on hypertensin, concluded that it represented a monomolecular reaction

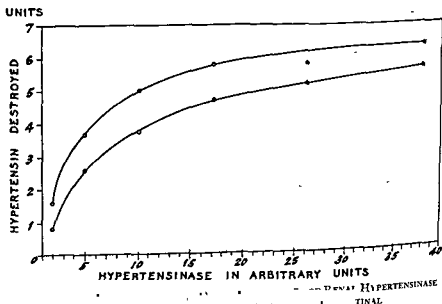
PREPARATION

Little progress has been made in the purification of hypertensinase From the kidney, it is easy to obtain renin free from hypertensinase but not hypertensinase free from renin. This is due to the fact that hypertensinase is easily destroyed and large losses occur at each step of purification. Marty-Calvo (1942) claimed that he obtained extremely active preparations of hypertensinase with negligible renin activity by fractional precipitation with acetone For the assay of hypertensin, he perfused the hind leg of the frog, which under these conditions gives unreliable results.

The best starting material for its preparation is probably red blood cells in which the hypertensinase is not accompanied by as many enzymes as other tissues contain. Up to the present, however, its separation from hemoglobin has not been successful.

ASSAY OF HYPERTENSINASE

Fasciolo, Leloir, Muñoz and Braun-Menéndez (1940b) described a method of assay of hypertensinase. The principle of this method *consisted of measuring the amount of hypertensin* remaining after



(After Fasciolo, Leloir, Muñoz, and Braun-Menéndez, Rev Soc. argent de biol, 1940, *16*, 643)

incubating a known quantity of hypertensin with the hypertensinase extract to be investigated. The relation between the destruction of hypertensin and the amount of hypertensinase in variable lengths

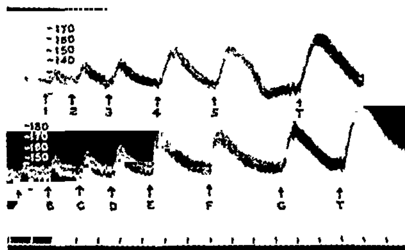


FIGURE 67 RELATION BETWEEN QUANTITY AND ACTIVITY OF HYPERTENSINASE FROM RED BLOOD CELLS

[illegible]

cc; (D) 0 51 cc; (E) 0 41 cc; (F) 0 31 cc.; (G) 0 24 cc, (T) 1 cc boiled (After Fasciolo, Leloir, Muñoz and Braun Menéndez, Rev Soc. argent. de biol, 1940, 16, 643)

of time was studied In order to avoid the use of protein precipitants, the amount of hypertensinase added was small and incubation periods prolonged. With long incubations, bacterial contamination which is capable of destroying hypertensin had to be prevented At the end of incubation, the reaction was interrupted by heating to 100°C. The solutions were assayed in the dog by measuring the amount of hypertensin remaining The technique finally adopted is described in the Appendix

[illegible]

Helmer, Kohlstaedt and Page (1912) and Helmer, Kohlstaedt.

Kempf and Page (1942) used a similar method except that it was buffered at a lower pH. The method was used for assaying renal hypertensinase which acts at a lower pH and was as follows: 1 cc of a solution of hypertensinase, 1 cc. of 5.0 M acetate buffer at pH 4, and 0.5 cc. of a solution of hypertensin (probably about 1 unit) were mixed These were incubated for 30 minutes at 37°C. and then boiled for 10 minutes and injected into the dog.

DETERMINATION IN BLOOD. Dexter (1942) modified slightly the method of Fasciolo and collaborators (1940b) for the assay of hypertensinase in plasma. The blood was withdrawn and mixed with 0 1

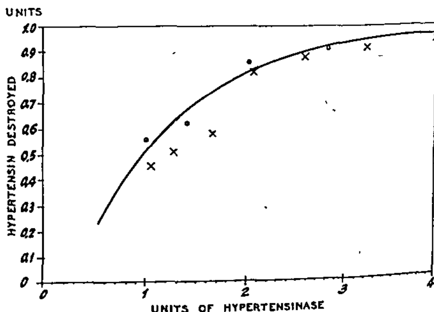


FIGURE 68 RELATION BETWEEN QUANTITY AND ACTIVITY OF HYPERTENSINASE FROM RED BLOOD CELLS

Curve plotted from data corresponding to figure 67. Arbitrary units (After Fasciolo, Leloir, Muñoz and Braun-Menéndez, Rev Soc argent. de biol, 1940, *16*, 643)

volume of a solution of 3.8 per cent sodium citrate and centrifuged The approximate amount of hemolysis in the plasma was determined by the benzidine test, by comparing the color obtained with that given by hemolyzed red cells in dilutions up to 1 in 40,000. Plasmas giving a greater amount of hemolysis than 1 in 5,000 were discarded All the pipettes, tubes and so forth were previously sterilized The

mixture of buffer, hypertensin and merthiolate was the same as that described by Fasciolo, Leloir, Muñoz and Braun-Menéndez (1940b) (see Appendix), but more concentrated, 8 cc. being used instead of 10

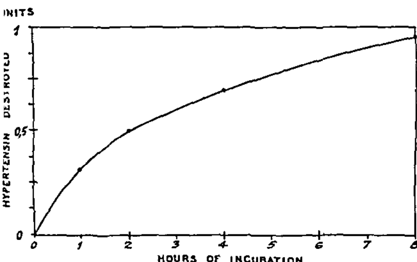


FIGURE 69 RELATION BETWEEN TIME OF INCUBATION AND ACTION OF HYPERTENSINASE

Ordinates, quantity of hypertensin destroyed by 0 65 unit of hypertensinase from red blood cells Abscissas, time of incubation in hours (After Fasciolo, Leloir, Muñoz and Braun-Menéndez, Rev Soc argent de biol 1940, *16*, 643)

cc. Eight cc. of the mixture were added to 7 test tubes and than 1.5, 1 0 and 0.5 cc of undiluted plasma, 1 5, 1.0 and 0 5cc of plasma diluted 4 times with distilled water The seventh tube was used as the control The volume of each tube was made up to 10 cc. It was incubated for 2 hours at 37°C and then heated to 100°C. for 10 minutes and injected into the dog. Dexter (1942) used an incubation time of 2 hours instead of 4 which was the time chosen by Fasciolo, Leloir Muñoz, and Braun-Menéndez (1940b). For calculating the units of hypertensinase, the empirical curves shown in figures 68 and 70 should be consulted

UNITAGE. Fasciolo, Leloir, Muñoz and Braun-Menéndez (1940b) defined the unit of hypertensinase as that amount which destroys 0 5 unit of hypertensin under the conditions described, i e., in 4 hours

at 37° C. at pH 7 4 in a volume of 10 cc. and with an initial amount of hypertensin of 1 unit. If exactly 0.5 unit of hypertensin is not destroyed in any of the tubes, the amount present can be calculated by referring to the curve shown in figure 68.

DISTRIBUTION OF HYPERTENSINASE IN DIFFERENT ORGANS

Fasciolo, Leloir, Muñoz and Braun-Menéndez (1940b) studied the content of hypertensinase in different organs of the dog. The results appear in table 3.

Organs with the highest content were the intestinal mucosa and the cortex of kidney. The pancreas, spleen, liver and hemolyzed red cells followed in decreasing order. Nonhemolyzed red cells had practically none, the small amount present possibly being due to a slight hemolysis It appears therefore that hypertensinase is not able to cross the red cell membrane Friedman, Marx and Lindner (1943) observed that the hypertensinase content of lymph was much less than that of plasma.

TABLE III HYPERTENSINASE CONTENT OF DIFFERENT ORGANS OF THE DOG
Units per gram of fresh tissue

Intestinal mucosa	1200–1600
Kidney	800
Intestine	400– 800
Pancreas	240
Spleen	160– 200
Hemolyzed red blood cells	80– 120
Liver	80
Adrenal	40– 50
Brain	4– 8
Heart	4
Nonhemolyzed red blood cells	4
Plasma or serum	1– 4

MECHANISM OF ACTION OF HYPERTENSINASE

Since the chemical composition of hypertensin is unknown, any interpretation of the mechanism of action of hypertensinase must be largely hypothetical. Certain evidence, however, suggests that hypertensin is a polypeptide, and since all known pressor substances are amines, it is logical also to suspect that its active group may be an amine. The action of different inhibitors on hypertensinase has also given information in regard to the group of enzymes to which it belongs.

also inhibit it. Cyanide (10^{-3} M) however does not inhibit its action.

Croxatto and Croxatto (1941a, b, d,) observed that crude extracts of Sepia officinalis containing an abundance of amine oxidase were capable of inactivating hypertensin. These investigators admitted that the action might be attributable to other enzymes in the impure mixture.

Octyl alcohol which inhibits amine oxidase does not inhibit hypertensinase (Bing, Zucker and Perkins, 1941; Croxatto, Croxatto and Marty, 1943).

(B) PHENOL OXIDASE. A number of enzymes are included in this category. One example is the polyphenol oxidase of potato, crystallized by Kubowitz (1937, 1938), the prosthetic group of which is copper. This enzyme oxidizes orthophenols such as catechol, adrenalin and dihydroxphenylalanine (Richter, 1934) to corresponding quinones. Some monophenols such as phenol and cresol are also oxidized, but only after an induction period. This type of enzyme has also been isolated from certain mushrooms As regards its presence in animal tissues, little is known at this time. Martin, Ichiowsky, Wisansky and Ansbacher (1942) observed that the destruction of adrenalin by purified tyrosinase was accelerated by ortho substituted phenols (catechol, cresol, amino phenol) and inhibited by aromatic amines and amino benzoic acids.

According to Schroeder and Adams (1941a, b), tyrosinase extracted from mushrooms can inactivate hypertensin *in vitro* as well as tyramine and adrenalin. Croxatto and Croxatto (1941c, d,) also observed inactivation of hypertensin by an extract of mushrooms with tyrosinase activity.

Bing, Zucker and Perkins (1941) obtained hypertensinase extracts which were inactive for hydroxytyramine, showing that hypertensin and hydroxytyramine are destroyed by different enzymes.

(C) PROTEOLYTIC ENZYMES. Hypertensin can be destroyed by certain commercial preparations of crystalline proteolytic enzymes such as pepsin and trypsin (Croxatto, 1943)

Croxatto and Croxatto (1942b) and Croxatto, Croxatto, Manríquez and Valenzuela (1942) studied the action of a purified preparation of amino polypeptidase from yeast. They observed that it destroyed

hypertensin as well as pepsitensin As a control they incubated amino polypeptidase with tyramine and adrenalin without obtaining any destructive action

With certain renal extracts containing hypertensinase, Sorolla (1942) and Croxatto, Croxatto and Sorolla (1942) obtained hydrolysis of *dl*-leucyl-glycine and also of *dl*-methyl-leucyl-diglycine, although with less speed Chloracetyl-tyrosine and carbobenzoxyglycylsarcosin were not attacked. This would therefore exclude the possibility that hypertensinase is a carboxypeptidase (see classification of Fruton, Irving, and Bergmann, 1941). This type of investigation is very interesting provided highly purified solutions of hypertensinase are used.

Croxatto and collaborators[1] compared the action of several enzymes on hypertensin, pitocin and pitressin Pepsin destroys hypertensin but not the pituitary hormone. Chymotrypsin destroys the three substances Trypsin destroys hypertensin and pitressin but pitocin only slowly They observed that extracts of kidney, liver and spleen destroyed pitressin only when substances with sulfhydryl groups were added (more details can be found in the publication of Croxatto, 1943)

According to Croxatto and Croxatto (1941a), during the destruction of hypertensin by hypertensinase there is a diminution of polypeptide nitrogen (soluble in trichloracetic acid but precipitated by phosphotungstic acid)

In conclusion it can be said that hypertensinase is not an oxidizing enzyme since it can act in the absence of oxygen. It differs from amine oxidase by not being inhibited by octyl alcohol and from phenol oxidase by not being unaffected by cyanide. It is therefore probably a hydrolytic enzyme It is also extremely probable that a number of enzymes are capable of destroying hypertensin

CONCENTRATION OF HYPERTENSINASE IN BLOOD IN DIFFERENT CONDITIONS

Muñoz, Braun Menéndez, Fasciolo and Leloir (1940) obtained ... which indicated that hypertensinase is diminished in dogs

[1] ...atto, Croxatto and Alliende, 1942, Croxatto, 1943, Croxatto, Croxatto, ...nd Silvestrini, 1943, Croxatto, Trautmann and Croxatto 1943 and

after nephrectomy. The same authors (Fasciolo, Leloir, Muñoz and Braun-Menéndez, 1940b), however, observed afterwards that the hypertensinase activity of serum or plasma depended on the degree of hemolysis in the blood Since hypertensinase in blood is found entirely or almost entirely in red cells, hemolysis produces a tremendous increase in its concentration in plasma The authors concluded that "this completely invalidates our previous observations since no precautions were taken to avoid hemolysis"

Dexter (1942) carried out new experiments in which, by taking into account the degree of hemolysis, no difference between the hypertensinase content of normal dogs and of those which had been nephrectomized 48 hours previously was encountered. No differences were found between normal dogs and dogs made hypertensive by renal ischemia

According to Friedman (1941), hypertensinase diminished as blood passed through an ischemic kidney. Hypertensin disappeared more rapidly when it was incubated with plasma from femoral blood than when it was incubated with plasma of venous blood from an ischemic kidney. The results were quite constant. The findings however might be interpreted in a different manner. The plasma which passed through the ischemic kidney contained renin. This renin would give rise to the formation of hypertensin, and the hypertensinase in these samples would have to destroy not only the hypertensin added but also that formed by the renin. This would result in an apparent diminution of destruction of hypertensin added to the plasma from ischemic blood in comparison with that from the systemic blood This interpretation is further suggested by the rises of pressure produced by plasma from the ischemic kidney incubated alone. These rises, although small, were greater than those produced by the plasma of the systemic blood

Weinstein, Friedman, Newman and Sugarman (1943) observed a diminution of hypertensinase in the venous blood from acutely ischemic kidneys which we have not been able to confirm. Quinby, Dexter, Sandmeyer, and Haynes (1945) observed no difference in the concentration of hypertensinase in renal arterial and venous blood of patients at operation before and after complete occlusion of the renal artery for periods of 10 to 12 minutes Incubation of the samples of plasma was carried out at both pH 7 3 and 4 5. Haynes and Dexter (1945) found normal values for hypertensinase in plasma

of patients with hypertension, liver and kidney disease, and a number of other disorders.

Extracts from tissues and blood possess the property of destroying hypertensin. The most active extracts are those of kidney, intestinal mucosa, liver and red blood cells This action is due to a substance which is thermolabile and not dialyzable It possesses the characteristics of a protein. This substance has been called hypertensinase. It is probable that there are many enzymes in the body which have the property of destroying hypertensin Most of the activity of the extracts is probably due to enzymes of a proteolytic nature, although other types of enzyme may well destroy hypertensin Hypertensinase may be assayed by incubating the solution to be investigated with a known quantity of hypertensin The unit of hypertensinase is defined as that amount which destroys 0.5 unit of hypertensin in four hours under certain conditions of pH and temperature.

Studies to date indicate that variations in the concentration of hypertensinase in plasma do not appear to influence the course of experimental renal hypertension

CHAPTER VIII

FORMATION, SECRETION AND DESTRUCTION OF RENIN IN THE BODY

I.—FORMATION OF RENIN

In this section we will discuss investigations which have been made concerning the portion of the kidney in which renin is stored or formed, its nature as it is found in the kidney, and the amount present in normal and pathological kidneys.

(A) ANATOMICAL SITE OF ORIGIN OF RENIN. In the region of the angle formed by the afferent and efferent arterioles of the glomeruli, there are certain anatomical structures which consist of the following: (a) the macula densa of Zimmerman This is a specialized segment of the distal convoluted tubule which is in intimate contact with the efferent arteriole in its juxtaglomerular portion. Within it there is an accumulation of cells which appear higher and are arranged in columnar form; (b) the juxtaglomerular apparatus which corresponds to a part of the wall of the afferent arteriole close to the glomerulus where the muscular cells of the medial layer are replaced by cells of epithelial character which are afibrillar and full of granules in many species of animals.

These structures are found in several mammals including man, in some birds and even in the frog. The afibrillar cells of the juxtaglomerular apparatus are observed not only in the afferent arteriole of the glomerulus but also in other small arteries of the kidney and other organs (Goormaghtigh, 1937; Goormaghtigh and Handovsky, 1938)

Elaut (1934) was the first to describe experimental changes in the juxtaglomerular apparatus. He observed hyperplasia of the afibrillar cells of the wall of the afferent arteriole in animals made hypertensive by section of the carotid and aortic nerves. He interpreted this finding as a defense mechanism of the body for the prevention of injury which an excess of blood pressure might produce within the

glomerulus Goormaghtigh and Handovsky (1938) observed in rabbits treated with large doses of Vitamin D, hyperplasia and an increase in the number of granular cells together with the hypertension. They also observed hyperplasia of the afibrillar cells in rabbits made hypertensive by renal ischemia (figure 71) which was subsequently confirmed (Dunihue and Candon, 1940; Dunihue, 1941). Although similar changes have been described in dogs with

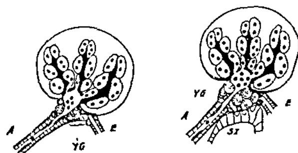


FIGURE 71 JUXTAGLOMERULAR APPARATUS AND RENAL ISCHEMIA

(A) afferent vessel; (E) efferent vessel, (YG) juxtaglomerular apparatus, (SI) intercalated segment. At the left, glomerulus from normal rabbit kidney; at the right, glomerulus of rabbit kidney after twenty-one days of slight ischemia Hypertrophy of the juxtaglomerular apparatus and increase in the number of granular cells (After Goormaghtigh, Brux Méd, 1939, *50*, 1541)

hypertension from renal ischemia (Goormaghtigh, 1939a, c, Goormaghtigh and Grimson, 1939; Goormaghtigh, 1940a), this finding has not been confirmed by other investigators, among them Goldblatt (personal communication) Kauffmann (1942) has recently described hyperplasia of the afibrillar cells in human kidneys of patients with hypertension from renal disturbances

As a result of these observations and the apparent cyclical activity of the granules of the afibrillar cells, Goormaghtigh (1939a, b, c) proposed the hypothesis that afibrillar and granular cells of the juxtaglomerular apparatus had an endocrine function and that they elaborated and secreted renin

There are certain objections to this hypothesis. First, unless these cells are preformed, which is apparently not the case in dogs, it is difficult to explain the immediate liberation of renin which follows partial ischemia of the kidney, and secondly, although similar cells are distributed in the arterioles of other organs (Goormaghtigh,

1937), renin is not liberated and hypertension is not produced by making them ischemic.

Friedman and Kaplan (1942) studied the renin content of fish kidneys in an effort to obtain information regarding the site of its formation Extracts of the glomerular kidneys of the carp, Cyprinus carpio, and the catfish, Ameurus nebulosus, both fresh water fish, were pressor in the dog while those from the aglomerular kidneys of the midshipman fish, Porichythys notatus, a marine fish, were not pressor. Since a grouping of cells at the pole of the glomerulus similar to the juxtaglomerular apparatus was observed in the kidneys of the former, the authors concluded that renin must be formed in the glomeruli or in adjacent structures and not in the tubules as had been suggested by Weeks, Steiner, Mansfield and Victor (1940) Later studies demonstrated that pressor substances were not obtainable from the glomerular kidneys of other marine fish, such as the cod fish, flounder (Kaplan and Friedman, 1942) and shark (Bean, 1942a, b), thereby raising serious doubts as to the validity of the previous conclusions

The same investigators studied the amount of renin contained in the kidneys of pig fetuses in different stages of development (Kaplan and Friedman, 1942). In the pig fetus the mesonephros undergoes a progressive degeneration with terminal metaplasia, while the metanephros increases in size and development. In the mesonephros of fetuses between 17 and 100 mm. of length, the tubules are degenerating while the glomeruli are little changed The amount of renin per gram of weight of the organ, however, diminishes as the fetus increases in length. In the metanephros, the tubules are at first underdeveloped in relation to the glomeruli. As the fetus grows, the development of the convoluted tubules is the chief factor responsible for the increasing size of the organ The concentration of renin in the metanephros increases with the age of the fetus as opposed to that which occurs in the mesonephros. It is evident that the amount of renin contained in the kidneys bears a relation to the number and size of the renal tubules and not to the development of the glomeruli. Juxtaglomerular cells such as those described by Goormaghtigh were not found in any of the kidneys

These investigations appear to indicate clearly that the afibrillar and granular cells of the juxtaglomerular apparatus are not the site of formation or storage of renin. They appear to indicate that these

functions are accomplished in the tubules. The tubular cells which absorb substances contained in their lumens and return them to the blood might well elaborate new substances and liberate them into the blood stream.

Friedman and Kaplan (1943) in a more recent publication, attempted to determine even more precisely the site of formation of renin by destroying localized areas of the kidney by the injection of chemical substances The subcutaneous administration of a solution of sodium tartrate (0 76 to 1.75 gm. per kgm. of body weight) into rabbits produced an extreme tubular necrosis within several hours This was limited mainly to the epithelium of the proximal convoluted tubules. The glomeruli were unaffected Friedman and Kaplan (1943) prepared extracts from these kidneys and found them to contain almost no renin These observations appear to indicate that the epithelium of the proximal convoluted tubule is mainly responsible for the formation or accumulation of renin

(B) STATE IN WHICH RENIN IS FOUND IN THE KIDNEY Studies performed on renin since the time of Tigerstedt and Bergman (1898) appear to demonstrate that renin is found in an active state rather than in an inactive one as in the case of certain other proteolytic enzymes in the body such as pepsinogen, trypsinogen, and so forth. Williams, Grollman and Harrison (1941), however, reported that by freezing and rapid drying they had at times obtained extracts which contained practically no pressor action but which became active after some time. They believed that the presence of renin in extracts obtained by usual procedures was due to enzymatic processes acting during the preparation. Marienfeld and Wakerlin (1943), found that sodium cyanide did not prevent the formation of renin in totally ischemic kidneys

We believe that this is still an unsolved problem. Until there are better methods for the extraction and quantitative determination of renin and a more precise knowledge of the various substances present in renal extracts, it is premature to draw definite conclusions.

(C) RENIN CONTENT OF KIDNEYS Several investigators have observed that saline extracts of ischemic kidneys from hypertensive dogs contain a greater pressor action than those from normal kidneys (Prinzmetal and Friedman, 1936, Harrison, Blalock, Mason, and

Williams, 1937; Prinzmetal, Friedman and Abramson, 1939; Williams, Grollman and Harrison, 1941). The same has been described in rabbits (Stollowsky, 1940) and man (Prinzmetal and Friedman, 1936; Prinzmetal, Friedman and Abramson, 1939). Pickering, Prinzmetal and Kelsall (1942) noted an increase in the renin content of ischemic kidneys of rabbits with subacute hypertension. In chronic hypertension the renin content was normal. Beckwith (1941) also found that the renin content of rat kidneys varied with the type of renal lesion (ligation of the pedicle or ligation of the ureter) and not with the time which had elapsed. In rats, Williams, Grollman and Harrison (1941) observed greater activity in normal kidneys than in ischemic kidneys, and Beckwith and Chanutin (1940) found less pressor action in the remnant of the kidneys of rats made hypertensive by partial nephrectomy than in the kidneys of control rats Others have found no difference in the pressor action of extracts of ischemic and normal kidneys of rabbits (Pickering and Prinzmetal, 1938b) and of man (Landis, 1941; Schales, 1942).

All these investigations are subject to serious criticism In the first place, the methods employed for the extraction and for the testing of renin activity are extremely unquantitative. In the second place, it is not known with certainty whether the time elapsing between the death of the animal and the preparation of the renal extract influences the amount of renin extracted The important point is not actually the amount of renin which the kidney contains, but rather the amount which it secretes.

II.—SECRETION OF RENIN BY THE KIDNEY

By using the methods described in Chapter IV for the determination of renin in blood it has been shown that acute or chronic partial occlusion and complete occlusion of the renal artery produce a liberation of renin. Let us consider the evidence on which this assertion is based. We will consider first the question of the presence of renin in the blood of hypertensive animals, and second the secretion of renin by the intact kidney.

(A) TOTALLY ISCHEMIC KIDNEYS. Re-establishment of the circulation through a kidney maintained in total ischemia by ligation of its pedicle produces a rise of blood pressure (Katzenstein, 1905). This observation was repeated by Dicker (1937d), confirmed and

amplified by Taquini (1938a, 1940) and has since been corroborated by several investigators[1] The time of ischemia necessary to produce a pressor response appears to be very short, according to Quinby and Simeone (1942) only three minutes. The time used by the majority of investigators has varied between ten minutes and six hours.

On re-establishing the circulation, the pressure increases and is elevated some 30 to 50 mm Hg in three to five minutes and stays at this level for twenty to thirty minutes (figure 72) (Dicker, 1937d, Taquini, 1938a) Denervation of the kidney, section of the vagi,



FIGURE 72 LIBERATION OF RENIN FROM COMPLETELY ISCHEMIC KIDNEY
The arrow indicates the time at which the circulation through one kidney was re-established after six hours of complete ischemia Time in minutes Blood pressure in mm Hg (After Taquini, Rev Soc argent de biol, 1938, *14*, 422)

destruction of the thoracolumbar cord, splenectomy or adrenalectomy do not prevent the rise of pressure (Collins and Hamilton, 1940b), and the injection of Fourneau 933 or of cocaine does not modify it (Prinzmetal, Lewis and Leo, 1940b).

The pressor action is due to a substance which is liberated by the kidney into the blood. If kidneys which have been in complete ischemia for six hours are grafted into the neck of nephrectomized or normal dogs, a rise of blood pressure is produced (figure 73) (Taquini, 1938a, 1940). Furthermore the injection of renal venous blood obtained after re-establishing the circulation of totally ischemic kidneys

[1] Collins and Hamilton, 1940a, Friedberg, Landowne and Rodbard, 1940, Collins and Hamilton, 1940b, Leo, Prinzmetal and Lewis, 1940, Prinzmetal, Lewis and Leo, 1940a, b; Lewis, Leo and Prinzmetal, 1941

produces the same pressor effect (figure 74) (Houssay, Braun-Menéndez, Fasciolo and Taquini, 1939). The citrated plasma of this



FIGURE 73 PRESSOR ACTION FROM GRAFT OF A COMPLETELY ISCHEMIC KIDNEY
Blood pressure in mm. Hg of a normal anesthetized dog. Time in minutes At (1), graft of a normal kidney; (2) removal of the graft; (3) graft of a kidney after six hours of complete ischemia (After Taquini, Rev. Soc. argent de biol, 1938. 14, 422).

blood also has a strong vasconstrictor action on the Läwen-Trendelenburg preparation (figure 75) (Taquini, 1938a, 1940).

A second injection into the same dog produces a less pronounced rise This phenomenon of tachyphylaxis can be demonstrated when the animal receives alternately the substance liberated by the kidney

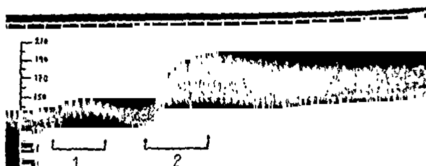


FIGURE 74 PRESSOR ACTION OF VENOUS BLOOD FROM A COMPLETELY ISCHEMIC KIDNEY
Effect of slow intravenous injection of 150 cc. of carotid blood (1) and of venous blood from a kidney completely ischemic for six hours (2) on the blood pressure of a 15 kgm chloralosed dog Time in minutes Blood pressure in mm Hg (After Houssay, Braun-Menéndez, Fasciolo and Taquini, Presse méd, 1939, 47, 810)

under these conditions and renin (Prinzmetal, Lewis and Leo, 1940b). If, for example, renin is injected previously, the pressor response to the re-establishment of the circulation through a totally ischemic kidney is less and, vice versa, if the injection of renin is made afterwards, its pressor action is less

From the form of the pressure curve, from its not being modified by Fourneau 933, cocaine, ergotamine, and so forth, from the vasoconstrictor action of the venous blood of totally ischemic kidneys, and from the phenomenon of tachyphylaxis, it can be assumed with

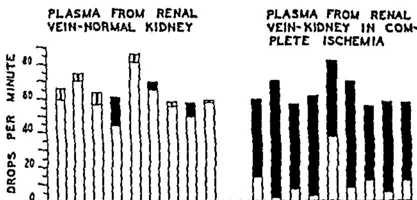


FIGURE 75. VASOCONSTRICTOR ACTION OF VENOUS BLOOD FROM A COMPLETELY ISCHEMIC KIDNEY

Action on the Lawen Trendelenburg preparation of the toad, *Bufo arenarum* Hensel Perfusion with citrated plasma of venous blood from normal kidneys and from kidneys after complete ischemia Each column represents the action of the plasma from the renal vein of one dog Black columns indicate diminution in the number of drops The striped columns indicate the increase in the number of drops Ordinates, number of drops issuing from the preparation per minute (From data of table 3 of Taquini, Rev Soc. argent. de biol, 1938, *14*, 422).

considerable confidence that the substance liberated from the kidney after several hours of total ischemia is renin

Prinzmetal, Lewis and Leo (1940b) perfused ischemic kidneys with Ringer's solution and showed that a substance appeared in the perfusing fluid with a pressor action similar to that of renin It was destroyed by boiling, and when incubated with plasma gave rise to the formation of a thermostable pressor substance These observations were confirmed by Taquini and Braun-Menéndez (1941) who identi-

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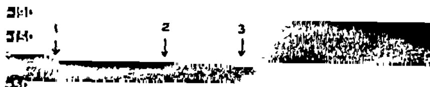


FIGURE 73 PRESSOR ACTION FROM GRAFT OF A COMPLETELY ISCHEMIC KIDNEY

Blood pressure in mm Hg of a normal anesthetized dog. Time in minutes At (1), graft of a normal kidney, (2) removal of the graft; (3) graft of a kidney after six hours of complete ischemia (After Taquini, Rev. Soc. argent de biol, 1938, 14, 422)

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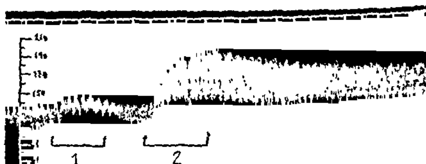


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From the form of the pressure curve, from its not being modified by Fourneau 933, cocaine, ergotamine, and so forth, from the vasoconstrictor action of the venous blood of totally ischemic kidneys, and from the phenomenon of tachyphylaxis, it can be assumed with

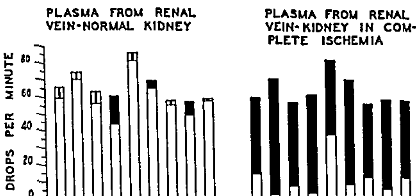


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fied the substance liberated from the kidney after total ischemia as renin. Finally, Taquini and Braun-Menéndez (1941) made quantitative determinations of the renin content of renal venous blood and of systemic arterial blood after re-establishing the circulation through totally ischemic kidneys. It was shown that the quantity of renin liberated by the kidneys under these conditions was great (figure 76). In one dog weighing 24 kgm., for example, approximately 1,000 units of renin were liberated during the first ten minutes following

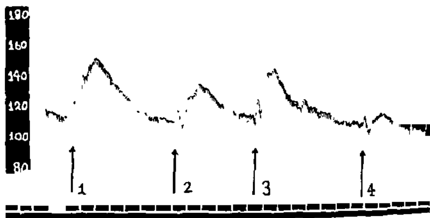


FIGURE 76 LIBERATION OF RENIN FROM A TOTALLY ISCHEMIC KIDNEY

Determination of renin in the carotid blood of a dog after re establishing the circulation of one kidney after complete ischemia for six hours. Effect on the blood pressure of an anesthetized dog of an intravenous injection of an alcoholic extract (1) of eight cc of beef plasma without hypertensinase incubated at 37°C for two hours with three cc of carotid plasma obtained twelve minutes after re-establishing the renal circulation; (2) the same with one cc. of carotid plasma, (3) one unit of hypertensin, (4) the same as (1) but with six cc of carotid plasma obtained before re-establishing the renal circulation Blood pressure in mm *Hg* (After Taquini and Braun-Menéndez, Rev. Soc. argent de biol , 1941, *17*, 465)

re-establishment of the circulation through a kidney which had been maintained totally ischemic for six hours. This amount is approximately five times greater than that necessary to produce a 40 mm. Hg rise of blood pressure in a 10 kgm. dog.

These observations demonstrate conclusively that the kidney, maintained for several hours in total ischemia by ligation of its pedicle, liberates an impressive amount of renin on re-establishing the circulation, with a resultant gradual and prolonged increase in blood pressure by the mechanism already described. A pressor sub-

stance other than renin may possibly be formed in the ischemic kidney, pass into the perfusing fluid and be differentiated from renin by being thermostable and soluble in alcohol (see Chapter XI)

(B) KIDNEYS IN PARTIAL ACUTE ISCHEMIA. With the identical procedures used for showing that the totally ischemic kidney liberates renin into the blood, it has been shown that the partially ischemic kidney liberates renin This is of importance since Goldblatt's method for producing permanent hypertension in dogs and other animals consists of partial constriction of the renal artery.

Partial ischemia of the kidney produces a moderate rise of blood pressure within a few minutes (Katzenstein, 1905, Enger, Linder and Sarre, 1938a) The first to observe this was Katzenstein (1905) but he attached little importance to it. After the discovery of Goldblatt and his collaborators, several investigators (Verney and Vogt, 1938, Samaan, 1936; Grimson, 1939) became interested in ascertaining the time elapsing between constriction of the renal artery and rise of pressure. Goldblatt and others who used this method observed that in some cases the pressure began to rise 24 hours after operation Since it was possible that this delay in pressor response was due to the actual operation, anethesia or infection, Verney and Vogt (1938, 1943) placed a pneumatic cuff connected to the outside by a rubber tube around the renal artery After the animal recovered from the operation, they partially occluded the artery by inflating the cuff and measured the blood pressure They found by this means that the pressure increased 20 to 30 mm Hg within 10 to 20 minutes

The experiments of Houssay and Fasciolo (1937a,b, 1938) had shown that a normal kidney graft into the neck of a recently nephrectomized dog did not produce an increase of pressure Braun-Menéndez and Fasciolo (1939a,b,) observed that if the artery of the graft was partially occluded, an immediate rise of pressure was obtained with characteristics similar to those produced by an injection of renin The same was observed when a kidney which had had its artery partially occluded for 30 to 90 minutes, was grafted into the neck of a nephrectomized or normal dog Under these circumstances, the renal venous blood acquired vasoconstrictor activity when perfused through Lawen-Trendelenburg preparations This blood, injected intravenously into anesthetized dogs, had a pressor action greater than that of normal control blood (Braun-Menéndez and

Fasciolo, 1939b; Friedman, Selzer and Sampson, 1941). The action was prolonged and unmodified by previous section of the carotid sinuses, adrenalectomy, or the injection of 1 mgm. per kgm. of atropine or 10 mgm. per kgm. of Fourneau 933 (Braun-Menéndez and Fasciolo, 1939b)

Alcohol and acetone extracts of this blood contained the thermostable pressor substance, hypertensin (Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1939, 1940a). If, however, the venous blood of partially ischemic kidneys was placed directly in acetone or maintained at a low temperature up to the moment of preparation of the extract, no hypertensin was found (Leloir, Muñoz, Braun-Menéndez and Fasciolo, 1940a). In other words, the blood which flowed from the ischemic kidneys contained a substance which, under the necessary conditions of pH, time and temperature, gave rise to the formation of hypertensin. The only known substance possessing this property is renin.

(C) ISCHEMIC KIDNEYS OF HYPERTENSIVE DOGS The first to demonstrate that ischemic kidneys of hypertensive dogs secrete a pressor substance were Houssay and Fasciolo (1937a, b) (see also Fasciolo, 1939, Fasciolo, Houssay and Taquini, 1938). These results were later confirmed by Dicker (1937d); Bouckaert, Grimson and Heymans (1939) and Govaerts and Muller (1939a). The graft of an ischemic kidney from one of these dogs into the neck of a nephrectomized dog produced a rise of pressure similar to that produced by an injection of renin The rise was gradual and prolonged The pressure did not fall immediately on removing the graft. If with the pressure still elevated another ischemic kidney was grafted, the pressure rose little if at all (tachyphylaxis). As in the case of renin, the grafting of ischemic kidneys produced a greater rise of pressure in nephrectomized animals than in normal controls

Houssay and Taquini (1938a, b) and Fasciolo, Houssay and Taquini (1938) demonstrated that the plasma obtained from the venous blood of these kidneys had an intense vasoconstrictor action on the Läwen-Trendelenburg preparation, while plasma of blood from normal kidneys was inactive. Goldblatt, Kahn and Lewis (1941) confirmed this finding with plasma of venous blood obtained from ischemic kidneys *in situ*. Mason and Rozzell (1939) were unable to demonstrate this action, possibly due to the use of serum instead of

citrated plasma, to technical difficulties, or to the use of a different animal species.

Page (1940a) produced hypertension in dogs with an ischemic kidney explanted underneath the skin of the flank He was thus able to extract samples of blood from the renal vein without anesthesia He found that the addition of hypertensinogen to the heparinized plasma of the renal venous blood caused vasoconstriction in the rabbit's ear The vasoconstrictor action was greater with venous blood from the ischemic kidney and less or none from the femoral blood of the same animal He concluded that renin secreted by the kidney disappeared as it was transformed into hypertensin (Page, 1941b). This interpretation is not in accord with the enzymatic properties of renin.

Dell'Oro and Braun-Menéndez (1942) performed similar experiments using the direct method of Leloir, Muñoz, Braun-Menéndez and Fasciolo (1940b) for the determination of renin They found no renin in the blood from the renal vein or from the blood of the femoral artery before producing renal ischemia Under ether anesthesia, they placed a Goldblatt clamp on the artery of an explanted kidney and induced a severe ischemia One, two or more days later when the pressure of the dog had risen 20 to 40 mm Hg above the initial level, new samples of blood were withdrawn Between 0 8 and 1 2 units of renin per 12 cc of plasma were detected both in the renal venous blood and in the femoral blood, although the amount in the latter was slightly less (figures 77 and 78)

Assuming that renin was the substance responsible for the production of hypertension of renal origin, we attempted to determine the amount of renin which could be found in the blood of a hypertensive dog For this purpose dogs were infused continuously with dilute solutions of renin. In a 10 kgm dog, the slow infusion of 0 02 cc (2 units) of a solution of renin per minute for 40 minutes produced a gradual rise of 20 mm Hg The pressure remained at this level until the infusion was stopped It then fell to the initial level in 10 minutes At the end of the infusion, 1 unit of renin was found in 20 cc of serum In another dog weighing 12 7 kgm and anesthetized with amytal, the infusion of a solution of renin at the rate of 0 026 cc (2 6 units) per minute for 30 minutes produced rise of 25 mm Hg The blood pressure remained elevated throughout the injection and fell to its initial level within a few minutes of

stopping the infusion. At the end of the injection, 0.22 unit of renin was found in 6 cc. of plasma. No renin was found in the urine After the pressure fell to the initial level, renin could no longer be detected in the blood. In another similar experiment renin was in jected at the rate of 0.02 cc. per minute for 35 minutes to a dog weighing 12 kgm. The pressure rose and was maintained at an elevated level during the infusion and returned to normal three minutes after infusion was stopped. At the end of the infusion there

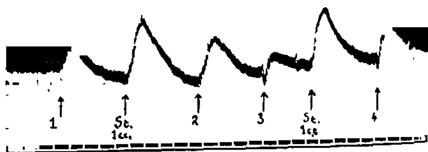


FIGURE 77 DETERMINATION OF RENIN IN BLOOD OF DOGS WITH HYPERTENSION FROM RENAL ISCHEMIA

Effect on blood pressure of an anesthetized dog from the intravenous injection of alcoholic extracts of twelve cc of plasma (hypertensinase previously destroyed) incubated for two hours at 37° C. with eight cc. of beef plasma without hypertensinase (1) femoral blood of hypertensive dog no 11 (figure 78); (4) renal venous blood of the same animal, (2) femoral blood of dog no 8 after renal ischemia, (3) renal venous blood of dog no. 15 before renal ischemia; St 1 cc. one unit of hypertensin. Interval between two horizontal dotted lines is equal to ten mm Hg Time in minutes (After Dell'Oro and Braun-Menéndez, Rev. Soc. argent. de biol., 1942, *18*, 65).

was 0.18 unit of renin in 6 cc. of plasma and three minutes later no renin was found.

These experiments show (1) that during the infusion of small amounts of renin the blood pressure may be maintained at an elevated level for a longer period than that resulting from a single injection of the same amount of renin; (2) that while the pressure is elevated renin can be detected in the blood and that when the pressure returns to its initial level after stopping the infusion, renin can no longer be detected in the blood.

The amount of renin found in these experiments was more or less the same as that found by Dell'Oro and Braun-Menéndez (1942) in dogs with explanted kidneys. In one of these dogs weighing 20

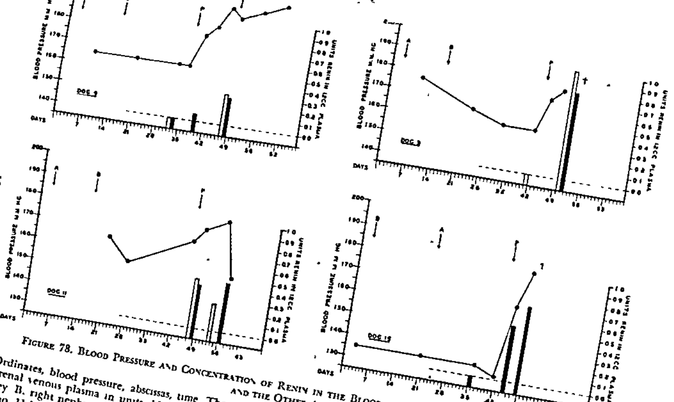


FIGURE 78. BLOOD PRESSURE AND CONCENTRATION OF RENIN IN THE BLOOD OF DOGS WITH ONE KIDNEY ISCHEMIC AND THE OTHER ABSENT

Ordinates, blood pressure, abscissas, time The curves indicate blood pressure, white columns, concentration of renin in the renal venous plasma in units, black columns, concentration of renin in the arterial plasma A. explantation of the left kidney B. right nephrectomy. P. constriction of the renal artery with a Goldblatt clamp. Cross indicates death of the animal. Dog no 11 had marked nitrogen retention. Dog no 15 died in convulsions (After Dell Oro and Braun Menéndez, Rev. Soc. argent de biol, 1942, 18, 65).

kgm with a blood pressure elevation of 30 mm. Hg two days after partial constriction of the renal artery, 1 unit of renin was found in 12 cc. of plasma from the femoral arterial blood This amount is actually very small. Assuming that this dog weighing 20 kgm. had 40 cc. of plasma per kgm., there would be only 66 units of renin in the circulating blood. It is to be noted that in order to produce a rise of 40 mm. Hg pressure it is necessary to inject 100 to 200 units intravenously at one time. Since such minute quantities of renin are present, it is understandable why so many attempts have failed to demonstrate pressor activity in the blood of hypertensive dogs (Collins and Hoffbauer, 1937; Katz, Friedman, Rodbard and Weinstein, 1939) and of hypertensive patients (Curtis, Moncrieff and Wright, 1927; Höst, 1931; Elliot and Nuzum, 1933; Leiter, 1936, Friedman and Prinzmetal, 1939) Solandt, Nassim and Cowan (1940) have been the only ones to observe, through the use of cross transfusions between hypertensive and nephrectomized dogs a transitory elevation of pressure in the recipient.

(D) PRESENCE OF RENIN IN THE BLOOD IN EXPERIMENTAL HYPERTENSION. We have discussed the evidence for conluding that totally ischemic kidneys liberate renin Subacute or acute partial ischemia also causes the kidney to liberate renin Many attempts to demonstrate the presence of renin in the systemic blood of dogs with chronic hypertension of the benign type have failed. In the experiments of Dell'Oro and Braun-Menéndez (1942), pronounced ischemia was produced which was associated with a gradual rise of blood pressure and the appearance of renin in the blood. The dogs died in four to eight days with the picture of renal insufficiency This was a study, therefore, of malignant hypertension Dexter and Haynes (personal communication) have detected renin in the systemic blood of dogs for several weeks after the induction of hypertension by constriction of the renal artery Although hypertension was maintained, the renin concentration gradually diminished and finally disappeared.

Why is it that we have not found renin in the blood of dogs with chronic benign hypertension of three months' to four years' duration and with a blood pressure of 180 to 240 mm. Hg? This problem which is of fundamental importance, and as yet unsolved has recently been discussed by Leloir, Braun-Menéndez, Dexter, Fasciolo,

Muñoz and Taquini (1945). It is possible that the amount of renin is extremely small and that our methods may not be of sufficient sensitivity to detect it. With the direct method of Leloir, Muñoz, Braun-Menéndez, and Fasciolo (1940b), a volume of plasma greater than 12 to 15 cc. can not be used It is possible that in this volume there is less than 1 unit of renin Even this, however, does not explain why such small amounts of renin produce such profound hypertension since, after the continuous injection of renin and in experimental malignant hypertension where larger amounts of renin are found in the blood (Dell'Oro and Braun-Menéndez, 1942), the rise of pressure is only 20 to 40 mm Hg It might be argued, perhaps, that in these experiments there were such other factors as impure renin or shock which partially suppressed the pressor action of renin It is also possible that in dogs with Goldblatt hypertension a greater sensitivity to renin develops or renin may be the initial cause of the hypertension followed by some other substance or substances which as yet are unknown. In this respect, the observations of Reed, Sapirstein, Southard and Ogden (1944) are of interest They showed that yohimbine, a sympatholytic agent, lowered the blood pressure of rats with chronic renal hypertension but did not lower their blood pressure in the early stages of hypertension

(E) SECRETION OF RENIN BY THE NORMAL KIDNEY

Evidence that the ischemic kidney secretes renin has been discussed Apart from ischemia, are there other conditions which cause the kidney to secrete renin? One casual observation suggested that in conditions of shock the intact kidney secretes renin In a study performed by Houssay, Braun-Menéndez and Dexter (1942), renin was detected in the blood after injecting it intravenously into dogs submitted to various procedures In general, the concentration of renin rapidly reached a maximum and then gradually diminished until it disappeared at the end of one to four hours In two of the control dogs in which a laparotomy had been done without removing the kidneys, the concentration of renin which had diminished in the first hour began to increase These dogs were in shock as indicated by a low blood pressure and deep respirations This interesting result led to a series of experiments performed by Huidobro and Braun-Menéndez (1942) in which they confirmed the previous observation Simultaneously and independently Sapirstein, Ogden and

Southard (1941) and Collins and Hamilton (1942) reached similar conclusions Sapirstein, Ogden and Southard (1941) detected renin by its action on the intestine, a method which has little specificity. Collins and Hamilton (1942) and Hamilton and Collins (1942a, b) assumed the presence of renin in the blood of their dogs from the pressor action of the blood and from the existence in these animals of a diminished sensitivity to injected renin. More recently, Dexter, Frank, Haynes, and Altschule (1943) using the direct method of Leloir, Muñoz, Braun-Menéndez, and Fasciolo (1940b) and Collins

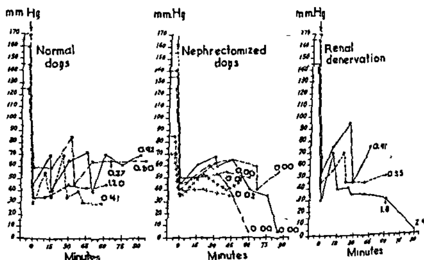


FIGURE 79 LIBERATION OF RENIN PRODUCED BY HEMORRHAGE

Ordinates, blood pressure; abscissas, time Figures on the curve indicate the units of renin contained at that moment in the plasma of anesthetized dogs after hemorrhage equivalent to four per cent [illegible] weight (From data of Huidobro and Braun-Menéndez, Am J. Physiol, [illegible])

and Hamilton (1944), using th[illegible] ileum, [illegible] intact animal for assay, found [illegible] increased sinog[illegible] in the blood o[illegible] [illegible]orrhagic Hu[illegible] Braun-[illegible] emplo[illegible] meth[illegible] Muñoz, [illegible] [illegible]d F[illegible] the [illegible] of renin in [illegible]ood [illegible] found [illegible] 2 4 [illegible] hyp[illegible] between [illegible] 79). H[illegible] produce[illegible]

to indicate that the *stimulus for the secretion of renin is not* tissue anoxia, since renin did *not appear* in the blood after breathing mixtures poor in oxygen or after poisoning with carbon monoxide or potassium *cyanide*. The *hypotension itself* may possibly be the effective *stimulus*, although it must be confessed that the *mechanism* by which it acts is obscure. *Second*, it is important to *recognize that* a more or less *prolonged* state of hypotension suffices to produce a *secretion* of renin by the *kidney*. This mechanism, for example, explains the diminution of hypertensinogen observed by Page, Mc-

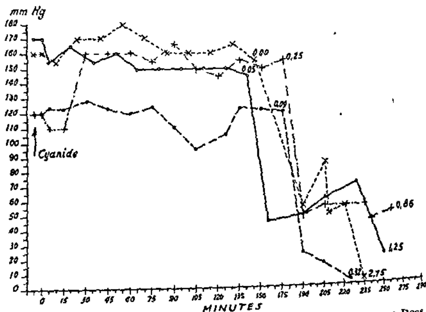


FIGURE 81 BLOOD PRESSURE AND RENIN CONTENT OF FEMORAL BLOOD OF DOGS INJECTED WITH KCN AND SUBSEQUENTLY SUBJECTED TO HEMORRHAGE

Ordinates, blood pressure in mm Hg, abscissas, time in minutes The figures along the curves indicate the units of renin in the plasma Dogs were injected with KCN (first arrow) and later submitted to hemorrhage equivalent to four per cent of body weight (After Huidobro and Braun-Menéndez, Am. J Physiol, 1942, *137*, 47).

Swain, Knapp and Andrus (1941) in hypotensive animals following hepatectomy and toxic hepatic lesions, and those observed by Houssay and Dexter (1942) and Goldblatt, Lewis and Kahn (1942) in adrenalectomized dogs, and the diminished sensitivity to renin of adrenalectomized dogs or dogs in shock (see Chapter V). Third, these experiments appear to demonstrate that the kidney is involved in the

homeostatic regulation of blood pressure. Hypotension not only engenders reflexes in the pressor receptors producing generalized vasoconstriction, tachycardia and a secretion of adrenalin, but also, by some mechanism as yet unknown, determines the secretion of renin by the kidney which, through forming hypertensin in the blood, contributes to the normalization of the blood pressure (Huidobro and Braun-Menéndez, 1942, Hamilton and Collins, 1942a, b). The normal blood pressure of nephrectomized dogs does not negate the rôle of the kidney in the regulation of blood pressure. Bilateral extirpation of the adrenal medulla does not produce a permanent fall of blood pressure and yet it can not be denied that the adrenal medulla is concerned in the regulation of blood pressure.

It is probable that there is a continuous secretion of renin as evidenced by the increase in hypertensinogen, the fall of blood pressure, and the hypersensitivity to renin and hypertensin found 24 to 48 hours after nephrectomy in dogs

It may be concluded that the kidney is a gland of internal secretion which participates in the regulation of blood pressure and that its product of secretion, renin, is one of the many physiologic substances which the body uses for maintaining its homeostasis

III.—MECHANISM OF THE SECRETION OF RENIN

We have stated that constriction of the renal artery produces a secretion of renin The method of Goldblatt, which consists of constricting the main renal artery by a clamp, and the method of Page (1939b, c), which consists of producing a perinephritis which compresses the kidney and probably narrows the renal arterioles, are the two methods most frequently employed for producing hypertension in animals Renin is secreted as a result of both procedures

Let us consider the stimuli which produce a secretion of renin. Theoretically the obvious hemodynamic disturbances resulting from constriction of the renal artery are diminution of mean blood pressure, of pulse pressure and of renal blood flow. Most investigators believe that diminution of blood flow, i e, renal ischemia, is the most important factor in producing a secretion of renin Diminution of blood flow can produce anoxemia or increase in carbon dioxide in the blood which bathes the tubules as well as other disturbances, the importance of which we do not know. On the basis of certain experimental observations which can not as yet be considered as

conclusive, and on the basis of clinical speculation, a preponderant rôle has been attributed to a diminution of pulse pressure.

RENAL ISCHEMIA: In *acute* experiments, there is no doubt but that diminution of renal blood flow, produced either by constriction of the renal artery (Leloir, Braun-Menéndez, Muñoz, and Fasciolo, 1940a) or by diminution of blood pressure (*Huidobro and Braun-Menéndez, 1942*), produces a liberation of renin In these experiments, renal ischemia is certainly extreme since it is accompanied by impairment of renal function. *Enger, Linder and Sarre* (*1938a*) found that after moderate constriction of the renal artery, renal blood flow diminished but rapidly returned to its initial level The elevation of pressure produced by this procedure, however, was maintained. Schroeder and Steele (1940) also observed that they could increase the constriction of the renal artery several times, the blood flow *each time* returning to its original value This they attributed to renal vasodilatation Levy, Light and Blalock (1938) were the only investigators to measure directly the renal blood flow in hypertensive dogs. Seventy-three days after constriction of the renal artery, the arterial pressure distal to the constricting clamp was 38 to 50 mm. Hg less than that in the femoral vessels and the blood flow was reduced by an average of 41 *per cent*.

Corcoran and Page (1938), utilizing phenol red and inulin clearances in dogs with moderate hypertension from constriction of the renal artery, found that in some cases hypertension existed without clearance changes They concluded that neither a reduction of intraglomerular pressure nor a decrease of renal blood flow was responsible and, therefore, considered that the hypertension must be due to some other factor. Subsequently, Corcoran and Page (1941a, 1942) used diodrast and inulin for the determination of renal blood flow and glomerular filtration They found it to be normal in a few hypertensive dogs following constriction of the renal artery or perinephritis. It is to be noted, however, that in the majority of the hypertensive dogs, the diodrast clearance was less than normal. These methods, although valuable, are indirect and we do not believe that the finding of a few isolated cases of hypertension with normal values for diodrast clearance indicates conclusively that renal ischemia did not cause the hypertension These authors did not determine in all cases the tubular excretory mass by diodrast at high concentration

with which, according to the studies of Smith and his collaborators, the diodrast clearance must be compared in order to determine whether or not the effective renal blood flow is diminished. The observations of Mason, Robinson and Blalock (1940), who found that the arterial pressure distal to the constriction of the renal artery in hypertensive dogs could be equal to that existing before the compression, and that its variations bore no direct relation to the level of the systemic blood pressure, also suggest that hypertension is not due to renal ischemia. From an analysis of their experiments, however, it appears that the mean pressure in the renal artery distal to the clamp reached a level equal to that of the femoral pressure before producing hypertension in only one of 15 experiments In some of the other animals, there was a certain tendency for the pressure to approach the initial level but it did not reach it

DIMINUTION OF PULSE PRESSURE Kohlstaedt and Page (1910a) perfused isolated dog kidneys in order to study the hemodynamic changes responsible for the secretion of renin Constriction of the rubber tube which led from the pump to the kidney produced a reduction of mean pressure, pulse pressure and blood flow The authors reduced the pulse pressure by constricting the tube and attempted to keep the mean pressure constant by increasing the output from the pump as well as its frequency They observed a rise of mean pressure which they attributed to constriction of the efferent glomerular arterioles

As a result of these experiments they concluded that the stimulus causing the secretion of renin was a reduction of pulse pressure and that as a result of this there was a reduction of renal blood flow, the latter appearing to be more the result than the cause of the liberation of renin (Kohlstaedt and Page, 1940a, Page and Corcoran, 1942) The conclusion reached by Kohlstaedt and Page that the stimulus for the secretion of renin is a reduction of pulse pressure is difficult to reach from their published experimental data In only one of 18 experiments in which the data are complete (Kohlstaedt and Page, 1940a) was the renal blood flow normal. In the other 17, the renal blood flow at the end of the experiment was much less than before constriction of the artery In the majority of cases this reduction was from 40 to 60 per cent Furthermore renin was always found in the blood before the constriction as judged by the constrictor effect of

the blood incubated with hypertensinogen on the vessels of the rabbit's ear Although the authors state that some two hours after constriction of the renal artery the vasoconstrictor effect was greater in intensity and duration, it is difficult to attribute the liberation of renin to the diminution in pulse pressure since there had already been a liberation of renin before constriction of the artery when the pulse pressure was normal If the amount of renin was greater after the constriction, which is difficult to measure accurately by the method employed, it is not clear why this should have been attributed to a diminution of pulse pressure since the blood flow had become appreciably reduced simultaneously. In order to attribute the observed increase of mean pressure to vasconstriction of the efferent glomerular arteriole, the output of the pump would have to remain perfectly constant. Since both blood flow and urine excretion diminished despite an increase of mean pressure, edema of the kidney may well have been present, since with constriction of the efferent arteriole, the excretion of urine should have increased.

We have performed numerous perfusion experiments on the isolated kidney in order to determine or at least clarify some of the factors which cause renin to be secreted. This organ must be perfused under such conditions that there is no liberation of renin before constriction of its artery. While we have succeeded in doing this in some cases, we have failed under seemingly identical conditions. Causes for the differences in behavior have not been explained Until the conditions under which perfused kidneys can be prevented from secreting renin are understood, it will be extremely difficult to determine the effect of different variants

ANOXEMIA; RENAL ANOXIA. Whether or not the ultimate cause of the secretion of renin and of the resultant hypertension is diminution of renal blood flow or reduction of pulse pressure, the most important factor to determine is the immediate cause. Are the cells which secrete renin sensitive to pressor or chemical stimuli, and if chemical is it due to a reduced tension of oxygen or to an increased tension of carbon dioxide or to other unknown stimuli? And do such causes lead to hemodynamic changes or to changes in cell permeability which result in the liberation of renin?

Goormaghtigh's hypothesis (1939a, b, c) attributing the secretion

of renin to the afibrillar and granular cells of the juxtaglomerular apparatus was in accord with the idea that a lowering of pressure in the afferent arteriole was the stimulus for those cells to secrete renin From the investigations of Friedman and Kaplan (1942, 1943), which appear to demonstrate the preponderant rôle of the tubular cells in the secretion of renin, it appears improbable that the reduction in pressure is the principal stimulus since variations of arterial pressure would become dampened by passage through the glomerular capillary.

The first chemical stimulus to be discussed is one of oxygen lack as a result of ischemia The experiments of Huidobro and Braun-Menéndez (1942) tend to exclude this as a probable mechanism Dogs were made to breathe mixtures of gases poor in oxygen (6 to 8 per cent) for periods up to one hour Even though the oxygen saturation of arterial blood was as low as 25 per cent, no renin was found in the peripheral blood as long as the blood pressure was maintained It is important to point out that these experiments are not conclusive since the accumulation of renin in the systemic blood, which is taken as an index of the secretion of renin, depends on the relation of its production by the kidney and its destruction in the body Be that as it may, anoxemia was not as efficacious as hypotension in producing an accumulation of renin in the blood, from which it is concluded that anoxia is not the main factor in the secretion of renin by the kidney Histotoxic anoxia produced by potassium cyanide and anoxemia by poisoning with carbon monoxide also did not produce an accumulation of renin in the blood The investigations of Steiner, Weeks and Barach (1940) appear to demonstrate also that the anoxemic factor is not particularly important Breathing of pure oxygen for 24 to 48 hours did not change the blood pressure of dogs made hypertensive by renal ischemia nor of hypertensive patients A continued elevation of blood pressure was not produced in dogs with constriction of the renal artery by the inhalation of mixtures with only 7 to 10 per cent of oxygen

Levy, Light and Blalock (1938) found that the arterio-venous oxygen difference of the kidney was not changed in hypertensive dogs despite a marked reduction of renal blood flow In other words, the consumption of oxygen by the kidney was reduced in equal proportion to the renal blood flow. Interpretation of these experiments is difficult It seems possible, however, that the kidney metab-

lism was reduced or that part of the renal tissue was not functioning or else that part of the blood was detoured by an arterio-venous shunt. Gerbi, Rubenstein and Goldblatt (1940) observed that the oxygen consumption of ischemic kidney tissue was less than that of normal kidney tissue in rabbits. This has recently been confirmed by Raska (1943) using the kidneys of hypertensive dogs Mason, Robinson and Blalock (1940) did not obtain the same results

Another possible stimulus would be an increase of carbon dioxide tension in or around the cells of the kidney. Breathing of mixtures of 2 to 5 per cent carbon dioxide, however, did not produce a demonstrable secretion of renin (Huidobro and Braun-Menéndez, 1942)

From the above discussion it is concluded that the actual cause for the secretion of renin has not been determined with certainty There is no doubt but that in the majority of cases of experimental hypertension there is a renal ischemia and an intrarenal hypotension If it should be proved conclusively, however, that hypertension can *be produced without altering mean pressure or renal blood flow,* one would then have to think that some other factor such as reduction of pulse pressure is capable by itself of producing the secretion of renin Regardless of whether the factor is a diminution of blood flow, mean pressure or pulse pressure, the most important point to ascertain is in what manner it acts on the kidney. If it is not by anoxia or by increase of carbon dioxide, it is possible that the diminution of pressure *in the capillaries which irrigate the tubular cells alter their* function or permeability in some fashion. All these hypotheses still require a considerable amount of investigation.

IV FATE OF RENIN IN THE BODY

Granted the important rôle which renin plays in the development of arterial hypertension, it is of importance to ascertain the mechanism *by which this substance is destroyed or* eliminated in the body. Several general techniques have been used for investigating this point· (a) search for renin in the urine after its injection; (b) study of the disappearance of renin in the blood after its injection into normal animals and those deprived of certain organs; (c) search for a substance in the blood capable of neutralizing or destroying renin, (d) study of the disappearance of renin from blood perfusing isolated

(A) ELIMINATION OF RENIN IN THE URINE. The investigations of Dexter and Braun-Menéndez (1941) and of Houssay, Braun-Menéndez and Dexter (1942) showed that the excretion of renin in the urine is not an important mechanism for its elimination from the body, since after the injection of 2 cc. of renin (80 units) to six dogs, in only one were even traces of this substance found in the urine. The injections of greater amounts resulted in easily demonstrable amounts of renin in the urine in all cases Between 6 and 42 per cent of the amount injected could be recovered We have not found renin in the urine of dogs or patients with hypertension

(B) DISAPPEARANCE OF RENIN FROM THE BLOOD. In order to study the disappearance of renin from the blood, Houssay, Braun-Menéndez and Dexter (1942) injected 80 units of renin into the jugular vein of anesthetized and unanesthetized dogs, and measured at intervals the concentration of renin in the blood by the direct method of Leloir and collaborators (1940b) In normal anesthetized and unanesthetized dogs, renin disappeared from the blood in less than 30 minutes The dose injected produced an elevation of 30 to 40 mm Hg of blood pressure which lasted 20 to 30 minutes It was observed that the concentration of the renin which had been injected coincided with its pressor action

In dogs nephrectomized one to three hours previously, renin disappeared from the circulation in about one hour In dogs nephrectomized 48 hours previously, on the other hand, small quantities of renin persisted for two to three hours after the injection of 80 units This indicated that there was some disturbance in the destruction or fixation of renin in uremia (figure 82).

In hepatectomized and nephrectomized and in eviscerated animals, renin disappeared from the blood in approximately the same time as in dogs recently nephrectomized These results led to the conclusion that except for the kidney, none of the abdominal organs played an important rôle in the destruction or elimination of injected renin, whereas its persistence in the blood of uremic dogs 48 hours after nephrectomy was attributed to a disturbance of the destructive or fixing action of the tissue This conclusion was modified by the subsequent investigation of Leloir, Muñoz, Taquini, Braun-Menéndez and Fasciolo (1942) After injecting 50 to 100 units of renin per kgm of body weight, a delay in the disappearance of

renin was observed in hepatectomized dogs. The liver, therefore, shares in the destruction of renin but this action becomes manifest only when large doses are injected.

From the experiments cited, it may be concluded (1) that the kidney plays some rôle in the disappearance of renin from the body since in normal dogs, injected renin disappears in about 30 minutes and in recently nephrectomized dogs, in one to two hours, (2) that the excretion of renin by the kidney does not explain the greater rapidity with which renin disappears from normal animals since

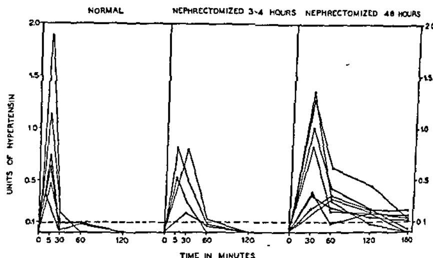


FIGURE 82 DISAPPEARANCE OF INJECTED RENIN

Concentration of renin in blood after the injection of two cc (80 units) of hog renin intravenously into unanesthetized normal, recently nephrectomized, and uremic dogs Results are expressed as units of hypertensin formed after two hours' incubation at 37°C of six to eight cc of plasma with hypertensinogen The method of assay was considered accurate to within 0 1 unit of hypertensin Values of less than 0 1 unit were therefore considered to be negative (After Houssay, Braun-Menéndez and Dexter, Ann Int. Med, 1942, *17*, 461)

renin is found in the urine only when amounts greater than 80 units are injected, (3) that apart from the kidney the only abdominal organ concerned with the destruction or elimination of renin is the liver since following the injection of a large dose of renin (50 to 100 units per kgm of body weight), this substance disappears more rapidly from nephrectomized dogs than from dogs that are nephrectomized and hepatectomized; (4) that although the kidney and liver are involved in the destruction, elimination or fixation of injected

renin, it is evident that the tissues in general play the more important rôle since with smaller doses of renin there is no appreciable difference between the time in which it disappears from the blood of nephrectomized dogs and of those which are nephrectomized and hepatectomized, or eviscerated

(C) NEUTRALIZATION OR DESTRUCTION OF RENIN BY THE BLOOD There may well be other mechanisms for the fixation or destruction of renin Since renin persists in the blood for such a long time in uremic dogs, it would seem possible that there is some substance in the blood of normal or recently nephrectomized dogs which neutralizes or destroys renin and gradually disappears or becomes absent in uremic dogs 48 hours after nephrectomy.

In order to investigate this, two types of experiments were performed In the first, 25 units of renin were added to 80 cc. of citrated blood obtained from the carotid artery of a normal dog. It was incubated for three hours at 37°C Samples were obtained at five minutes and at intervals of one, two and three hours, and their renin content determined. No diminution was found in the amount of renin in any of the samples, indicating that renin was not adsorbed on red cells nor was it destroyed or inactivated by any principle existing in this blood By this technique it was shown that renin was not destroyed by blood obtained from the jugular, suprahepatic or renal veins of normal dogs, nor by blood which had circulated for variable lengths of time through isolated livers or kidneys perfused with the heart-lung preparation (Houssay, Braun-Menéndez and Dexter, 1942).

The second type of experiment was performed with the purpose of ascertaining if the delay in the disappearance of renin from the blood of dogs nephrectomized 48 hours previously was due to an alteration on the part of the tissues or to the presence of some factor in the blood The blood of uremic dogs nephrectomized 48 hours previously was transfused into normal dogs and vice versa. One hundred and twenty units of renin were then injected into both animals The time elapsing before its disappearance from the blood was measured In the nephrectomized dogs transfused with normal dog blood, renin disappeared in three to five hours, and in the normal dog with uremic blood in less than three hours (figure 83) From these experiments is was concluded that the delay in the disappearance of renin observed in the uremic dogs after nephrectomy de-

pended upon a disturbance in the ability of the tissues to fix or destroy renin and not on the absence of some blood factor (Houssay, Braun-Menéndez and Dexter, 1942).

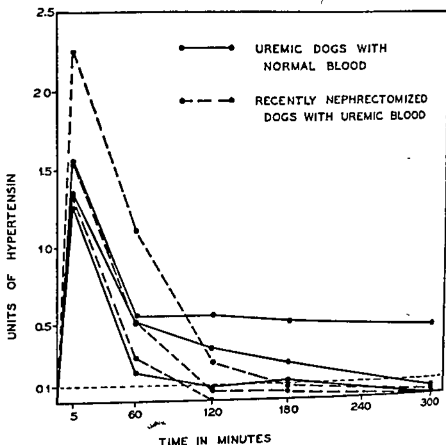


FIGURE 83 DISAPPEARANCE OF INJECTED RENIN

Concentration of renin in blood after the injection of three cc (120 units) of hog renin intravenously into uremic dogs transfused with normal blood and recently nephrectomized dogs transfused with uremic blood Results are expressed as units of hypertensin formed after two hours' incubation at 37°C with hypertensinogen The method of assay was considered accurate to within 0 1 unit of hypertensin Values of less than 0 1 unit were therefore considered to be negative Observe that renin disappeared at an essentially normal rate from the blood of normal dogs with uremic blood and slowly from uremic dogs with normal blood (After Houssay, Braun-Menéndez, and Dexter, Ann Int Med, 1942, *17*, 461)

Arterial hypotension as a result of hemorrhage or shock produces a secretion of renin by the kidney, renin being detectable in the systemic blood. The kidney can be considered as a gland of internal secretion which shares in the regulation of blood pressure. When the blood pressure falls, the kidney secretes renin which through the formation of hypertensin tends to re-establish the normal level of blood pressure. Renin is, therefore, one of the physiologic substances which the body uses to maintain its homeostasis.

The stimulus which produces a secretion of renin is still not known with certainty. Diminution of pulse pressure and changes resulting from renal ischemia (reduced blood flow) are the two most common factors incriminated. The latter has more cogent evidence in its favor

Injected renin disappears rapidly from the blood, and is either fixed or destroyed by the tissues throughout the body. Of the abdominal organs, the kidney and liver are the only ones that are involved to any appreciable extent in the mechanism which causes renin to disappear.

nution of renal blood low without an increase in the arterio-venous oxygen difference in the ischemic kidneys of hypertensive dogs, and by those of Gerbi, Rubenstein and Goldblatt (1940) and Raska (1943) who observed that slices of ischemic kidneys consumed less oxygen than normal.

The hypothesis of Pickering and Prinzmetal would explain the elevation of blood pressure resulting from removal of the normal kidney, leaving the ischemic kidney alone to do the work of both. Constriction of the renal artery of one kidney, the other kidney remaining intact, would produce a disproportion between the work

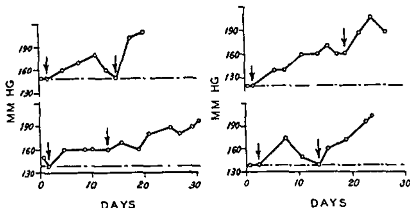


FIGURE 84 EFFECTS OF REMOVAL OF NORMAL KIDNEY ON THE BLOOD PRESSURE OF DOGS WITH UNILATERAL RENAL ISCHEMIA

performed by the kidney and its blood supply Under these circumstances the kidney would liberate renin with a consequent increase in blood pressure The hypertension would not be pronounced nor would it appear rapidly because the destruction of renin remains unaltered in the absence of uremia, and secondly because some of it is probably either excreted or destroyed by the normal function of the other kidney The ischemic kidney would gradually become adapted to the new conditions, transferring part of its work to the normal kidney The ischemic kidney which usually becomes smaller

produce a rise of pressure which is greater in nephrectomized than in normal dogs.

None of these observations actually prove a protective action of the normal kidney. Some maintain that animals recently nephrectomized rarely show an increase of sensitivity to renin. The greater and more prolonged pressor response to renin of nephrectomized uremic dogs is perhaps attributable to the persistence of renin in the blood for a greater length of time (Houssay, Braun-Menéndez and Dexter, 1942), to an increase of hypertensinogen in the plasma (Muñoz, Braun-Menéndez, Fasciolo and Leloir, 1940), and to a hypersensitivity of the vessels to hypertensin (Page and Helmer, 1940b; Rodbard, 1941; Houssay and Dexter, 1942).

ACTION OF THE NORMAL KIDNEY ON HYPERTENSION FROM RENAL ISCHEMIA

The second point favoring the belief that there is a protective action of the normal kidney is that although a rise of blood pressure may be obtained by constricting the artery of one of the kidneys and leaving the other intact (Goldblatt, Lynch, Hanzal and Summerville, 1934; Goldblatt, 1937a), the rise obtained is slight (Fasciolo, 1938a, 1939), less rapid (Fasciolo, 1938a, 1939), and usually transitory (Goldblatt, 1937a, 1938b, 1940). If the normal kidney is removed when the blood pressure is falling, the pressure rapidly rises to a higher level and becomes sustained (figure 84)

Pickering and Prinzmetal (1938b) found that a marked hypertension was rarely produced in rabbits by constriction of one renal artery leaving the other kidney intact. Anatomically there was atrophy of the ischemic kidney and enlargement of the normal kidney This observation led them to suggest that when the supply of blood to one kidney is reduced, the work which this kidney is incapable of performing can be transferred to the normal kidney. The ischemic kidney would perhaps reduce its oxygen consumption and its demand for blood.

As a result of these experiments Pickering and Prinzmetal suggested that the stimulus for the increase of blood pressure might be due to a disturbance in the normal relation between the supply of blood and demand for blood by the kidney, rather than to a simple ischemia This hypothesis was strengthened by the experiments of Levy, Light and Blalock (1938) who observed that there was a dimi-

nution of renal blood low without an increase in the arterio-venous oxygen difference in the ischemic kidneys of hypertensive dogs, and by those of Gerbi, Rubenstein and Goldblatt (1940) and Raska (1943) who observed that slices of ischemic kidneys consumed less oxygen than normal.

The hypothesis of Pickering and Prinzmetal would explain the elevation of blood pressure resulting from removal of the normal kidney, leaving the ischemic kidney alone to do the work of both. Constriction of the renal artery of one kidney, the other kidney remaining intact, would produce a disproportion between the work

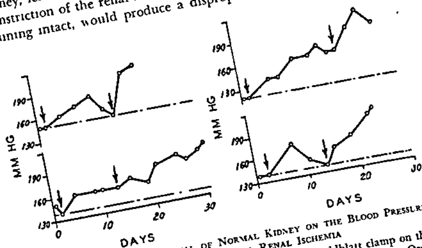


FIGURE 84 EFFECTS OF REMOVAL OF NORMAL KIDNEY ON THE BLOOD PRESSURE OF DOGS WITH UNILATERAL RENAL ISCHEMIA

The first arrow indicates the time of application of a Goldblatt clamp on the left renal artery The second arrow indicates removal of the right kidney. Ordinates, blood pressure in mm Hg The dotted line indicates the level of the initial blood pressure (Modified from Fasciolo, 1939)

performed by the kidney and its blood supply Under these circumstances the kidney would liberate renin with a consequent increase in blood pressure The hypertension would not be pronounced nor would it appear rapidly because the destruction of renin remains unaltered in the absence of uremia, and secondly because some of it is probably either excreted or destroyed by the normal function of the other kidney The ischemic kidney would gradually become adapted to the new conditions, transferring part of its work to the normal kidney The ischemic kidney which usually becomes smaller

with time, would then receive an adequate blood supply for its reduced function. As a result, it would stop secreting renin and the blood pressure would fall. It is probable that the development of a collateral circulation would contribute to this phenomenon. If at this time the normal kidney, which by now is hypertrophied, is removed, renal function would have to be accomplished entirely by the kidney with the constricted artery which would thereupon become ischemic again provided that its blood supply were too small for its functional demands. A secretion of renin would again be produced perhaps in larger amounts because the ischemia in relation to its function would be even greater than before. The blood pressure would become elevated. Unless a considerable collateral circulation should develop, the hypertension would be permanent because the kidney would be unable to adjust its supply of blood to the demand on its function for the reason that it could not limit its function without an ensuing renal insufficiency nor increase its blood supply due to the mechanical obstruction.

Unfortunately we have no information concerning the stimulus which produces compensatory hypertrophy of the remaining kidney and how it acts in cases of unilateral nephrectomy. White, Heinbecker and Rolf (1941, 1942) showed that compensatory hypertrophy of the remaining kidney did not occur after hypophysectomy. Zeckwer (1944) advanced evidence suggesting that renal hypertrophy was not dependent on the acidophilic cells of the pituitary gland. We do not know why this hypertrophy is preceded by about a 50 per cent increase of renal blood flow (Smith, 1937; Welsh, Wellen and Taylor, 1944)

TIME ELAPSING BETWEEN REMOVAL OF THE ISCHEMIC KIDNEY AND FALL OF BLOOD PRESSURE TO NORMAL

The third argument in favor of the belief that the normal kidney exerts a protective action is based on the observations of Rodbard and Katz (Rodbard, 1939; Rodbard and Katz, 1939, 1941) These authors observed that removal of the ischemic kidney in hypertensive dogs with the opposite kidney normal and *in situ* produced a return of blood pressure to normal levels within six hours. Removal of the ischemic kidney in hypertensive dogs, in which the normal kidney had previously been removed, was followed by a much slower return to the normal prehypertensive level.

Such a difference in the time element might perhaps be explained by the elimination of renin in the urine These investigators, however, observed that in dogs in which the ureter of the normal kidney was anastomosed to the lumbar vein, extirpation of the ischemic kidney produced the blood pressure fall just as rapidly as in animals with a normal intact kidney (Rodbard and Katz, 1941) From these observations, Rodbard and Katz (1941) concluded that the chemical mediator of experimental hypertension is destroyed by the metabolic activity of the normal kidney.

The marked differences observed by these investigators in the time of fall of the blood pressure on removal of the ischemic kidney with and without an opposite, intact, normal kidney was not observed by Blalock and Levy (1937) nor by Verney and Vogt (1938) This discrepancy may possibly have been due to differences in criteria adopted for establishing the exact moment when the normal prehypertensive blood pressure level was reached, or possibly to the fact that Blalock and Levy (1937) and Verney and Vogt (1938) followed the variations of mean pressure while Rodbard and Katz followed the variations of diastolic pressure The difference in time observed by Rodbard and Katz between the two groups of animals may possibly have been due to the lower level of pressure in the group with one kidney ischemic and the opposite normal kidney intact, and secondly to the possible presence of uremia in the hypertensive dogs with one kidney ischemic and the opposite kidney absent In this regard, Houssay, Braun-Menéndez and Dexter (1942) demonstrated that uremia markedly diminishes the capacity of the body to destroy renin. In any event, the observations of Rodbard and Katz are important and deserve further study

SECRETION OF NEUTRALIZING OR DEPRESSOR SUBSTANCES

Finally, it has been suggested that the normal kidney secretes a substance which in some manner neutralizes the effects of renin. It has been supposed that this substance is present in renal extracts.

INHIBITOR OF RENIN Page and Helmer (1940b) claimed to have demonstrated the presence of a renin inhibitor which appeared when a sufficient amount of renin was injected into a normal animal. One of their points of evidence in favor of this hypothesis was the

when plasma of a tachyphylactic dog, which was supposed to contain renin, was mixed with renin-activator (hypertensinogen), no vasoconstriction appeared when it was perfused through the isolated rabbit's ear. We have repeatedly found that the plasma of a dog injected with renin contains renin, especially if this substance has been injected in large amounts In order to measure it, however, the hypertensinase activity of the blood and possibly in the solutions of impure renin must be borne in mind This hypertensinase will destroy the hypertensin formed when hypertensinogen is added to the plasma containing renin unless precautions are taken to inactivate it by previously acidifying the plasma or by some other suitable procedure

In order to substantiate the hypothesis that an inhibitor of renin exists, Page (1940c) mentioned further experiments which showed that the hypersensitivity to renin of bilaterally nephrectomized dogs was reduced or suppressed by the transfusion of large amounts of blood of normal animals or of animals made tachyphylactic to renin Their interpretation does not appear to us entirely justifiable. The hypersensitivity to renin of uremic dogs is due in part at least to the increase of hypertensinogen in the blood. The substitution of blood rich in hypertensinogen for normal blood containing less hypertensinogen or for blood of dogs tachyphylactic to renin where the hypertensinogen is practically absent may well have been the cause of the diminished sensitivity to renin. Furthermore, the blood of tachyphylactic dogs contains so much renin that its transfusion is equivalent to the injection of this substance and, therefore, a new injection would produce less pressor response. We see no evidence in these experiments for the transference of inhibitor from one animal to another Actually it would appear more likely that there was a transference of renin from one animal to the other. We have been unable to discover any substance in blood which when incubated with renin destroys it, neutralizes it or inhibits its action (see Chapter VIII).

DEPRESSOR SUBSTANCE. Grollman, Harrison and Williams (1940c) suggested the possibility that the ischemic kidney lacks some substance which normally prevents the appearance of hypertension These authors observed (a) that the blood pressure of hypertensive rats fell to normal during the latter part of pregnancy and (b) that pregnant rats were more sensitive to renin than nonpregnant animals

These differences were attributed to the compensatory action of the fetal kidneys and would support the hypothesis formulated. In more recent publications, Grollman, Harrison and Williams (1943) and Grollman (1945) presented new evidence in favor of the hypothesis that hypertension is caused by the absence of a depressor substance normally secreted by the kidney They pointed out that in the rat and rabbit unilateral nephrectomy produces in some cases a slight increase of blood pressure. It should be noted, however, (1) that the rise observed was inconstant and slight; (2) that unilateral renal ischemia produced a much greater and much more prolonged rise of pressure than unilateral nephrectomy in the majority of cases, which should not have occurred if the hypothesis of these authors is correct; and (3) that in the dog unilateral nephrectomy does not produce changes of blood pressure.

Further evidence offered for this hypothesis was that in the rat *with hypertension from unilateral perinephritis, removal of the peri*nephritic kidney was not followed in all cases by a fall of pressure to normal levels This may well have been due to the appearance of irreversible lesions in the other kidney with a resultant persistence of hypertension as Wilson and Byrom (1941) and others have described Grollman, Harrison and Williams (1943) have observed that removal of the remaining kidney does not produce a fall of pressure to normal levels and that bilateral nephrectomy produces in normal rats a slight rise of blood pressure The evidence presented by Grollman and his collaborators is not in our opinion sufficient to prove their hypothesis Their findings may well be due to other factors such as an insufficient destruction of the pressor substance by the co-existence of uremia It is even possible that the changes in blood pressure observed depend on reflexes or some other mechanism rather than on humoral mechanisms of renal origin The fact that some of the changes observed by them do not occur in dogs is strong evidence against acceptance of their hypothesis

DEPRESSOR ACTION OF RENAL EXTRACTS. The action of renal extracts provides the main argument in favor of the existence of an antipressor substance secreted by the normal kidney Grollman, Williams and Harrison (1940a, b), Harrison, Grollman and Williams (1940), Williams, Harrison and Grollman (1940), and Grollman, Harrison and Williams (1940c) demonstrated first that the blood

when plasma of a tachyphylactic dog, which was supposed to contain renin, was mixed with renin-activator (hypertensinogen), no vasoconstriction appeared when it was perfused through the isolated rabbit's ear. We have repeatedly found that the plasma of a dog injected with renin contains renin, especially if this substance has been injected in large amounts. In order to measure it, however, the hypertensinase activity of the blood and possibly in the solutions of impure renin must be borne in mind This hypertensinase will destroy the hypertensin formed when hypertensinogen is added to the plasma containing renin unless precautions are taken to inactivate it by previously acidifying the plasma or by some other suitable procedure.

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action of the normal kidney must be used in the sense that the presence of a normal kidney in the body makes difficult the establishment of a *persistent and marked hypertension* They can not at present be used for suggesting the existence of a specific antipressor or antirenin activity of this organ since such an action has not been conclusively demonstrated

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In the dog the presence of a normal kidney in the body either dampens or prevents the establishment of permanent and marked arterial hypertension when the other kidney is made partially ischemic On removing the normal kidney, the blood pressure rises and remains elevated It is concluded from these observations that the normal kidney exercises a protective action on renal hypertension. Other arguments in favor of this protective action are the greater *sensitivity of nephrectomized dogs to renin, the influence which the* presence of a normal kidney has on the time which elapses before the pressure of a hypertensive dog becomes normal on removing the ischemic kidney, formation by the kidney of hypothetical hypotensive substances, inhibitors or neutralizers of renin, and a depressor action of renal extracts

After analyzing in detail the evidence at hand, it is concluded that there is no conclusive evidence for the presence in the kidney, or of a secretion by the same, of a neutralizing or inhibiting substance against renin, or for the renal secretion of a specific hypotensive substance The so-called protective action of the normal kidney may be attributable (a) perhaps to an elimination of renin in the urine, (b) perhaps to the metabolism or destruction of renin by the kidney as well as by *other tissues, (c) to the assumption of the function of the* ischemic kidney by the normal kidney, and (d) to the prevention of uremia which can aggravate hypertension by interfering with the destruction of renin by the tissues

pressure of hypertensive rats may be reduced to normal levels by the injection or oral administration of extracts of renal tissue. The intraperitoneal administration of these extracts, however, produced toxic symptoms which according to the authors were due to the presence of noxious substances.

Page and collaborators[4] also prepared extracts of kidney, muscle and lung which, when injected into dogs or rats with experimental hypertension, produced falls of blood pressure to normal levels. The renal extracts also had the same effect in patients with malignant hypertension According to the authors, the intramuscular injection of such extracts was not followed by toxic reactions such as occurred with the preparations of Grollman. Their effect on blood pressure was first a more or less marked elevation followed by a gradual fall until a normal level was reached in the course of six to eight days

It should be pointed out that treatment of human hypertension with renal extracts is not new. Dadlez and Koskowski (1934a, b) treated hypertensive patients with alcoholic extracts of kidneys and obtained prolonged falls of blood pressure. Gómez (1934a. b) also prepared extracts which when administered subcutaneously or intramuscularly produced falls of blood pressure in hypertensive patients but not in normal patients Jablons (1938) reported the beneficial effect of a renal extract which he called tubulin. In Chapter XVI, the possibility that the action of renal extracts is nonspecific is discussed in detail.

We have covered the main points in favor of the so-called protective action of the normal kidney in counteracting the substance responsible for hypertension from renal ischemia. The normal kidney may protect the body against hypertension in several ways (1) It may perhaps eliminate renin in the urine (2) It may perhaps metabolize or destroy renin as do other tissues (3) It may assume part of the function of the ischemic kidney. (4) It may prevent uremia which is capable of aggravating hypertension by disturbing the destructive action of renin by the tissues. We know of no conclusive evidence pointing to the presence of a substance inhibiting renin or to a substance in the kidney or its secretions, the absence of which is responsible for hypertension. The terms protective or neutralizing

[4] Corcoran, Kohlstaedt and Page, 1941b, Page, Helmer, Kohlstaedt, Fouts and Kempf, 1941, Page, Helmer, Kohlstaedt, Kempf, Gambill and Taylor, 1941.

The rôle of the adrenal cortex has been more difficult to investigate. Bilateral adrenalectomy produces death within a few days with the well known syndrome of asthenia and hypotension. It is extremely difficult to ascertain whether the fall of blood pressure observed in hypertensive animals is due to a lack of a specific substance of the gland or to terminal phenomena dependent upon the poor general

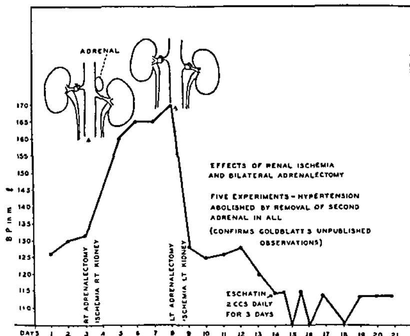


FIGURE 85 EFFECT ON BLOOD PRESSURE OF BILATERAL ADRENALECTOMY AND RENAL ISCHEMIA

Effect on the blood pressure of removal of both adrenals combined with bilateral *renal ischemia* *Observe the rapid fall of blood pressure following removal* of the second adrenal gland (After Blalock and Levy, Ann Surg, 1937, *106*, 826)

condition of the animal Goldblatt (1937a) showed that constriction of the renal arteries in adrenalectomized dogs did not produce a rise of blood pressure If hypertension had been produced previously, removal of the adrenals resulted in a fall of pressure. The administration of sodium chloride with sodium bicarbonate or sodium citrate prolonged the life of the adrenalectomized animals but was not capa-

CHAPTER X

INFLUENCE OF ENDOCRINE GLANDS AND OF PREGNANCY ON EXPERIMENTAL HYPERTENSION

It appears to us appropriate to include in the same chapter a discussion on the influence of endocrine glands and the state of pregnancy on experimental hypertension produced by renal ischemia The inclusion of pregnancy in this chapter seems justified because aside from hemodynamic changes occurring as a result of pregnancy, there is a hormonal imbalance in the body, a hormonal activity of placental origin, and even the possibility of fetal glandular activity.

INFLUENCE OF ENDOCRINE GLANDS

Since some endocrine glands can produce changes in blood pressure, it is important to study their possible rôle in the production of experimental renal hypertension.

ADRENALS AND HYPERTENSION. In discussing the action of the adrenals, the two parts of the gland must be considered separately. The medulla secretes adrenalin and its absence is compatible with life The cortex is necessary for life. Its removal produces severe and serious changes and causes the death of the animal in a matter of a few days unless adequate substitution therapy is instituted

The action of the adrenal medulla was first studied by Goldblatt, Lynch, Hanzal and Summerville (1934) who observed that constriction of the renal artery produced a marked elevation of blood pressure in two dogs in which the whole right adrenal and the left adrenal medulla had been removed, and the left adrenal denervated by section of the splanchnics on that side These findings were confirmed by Fasciolo (1938b) and by Page (1938). Rogoff, Marcus and Wasserman (1938) were unable to demonstrate an increase in the secretion of adrenalin in dogs made hypertensive by constriction of the renal artery. From these findings, it may be concluded that the adrenal medulla plays no important rôle in the production or maintenance of hypertension from renal ischemia

The rôle of the adrenal cortex has been more difficult to investigate. Bilateral adrenalectomy produces death within a few days with the well known syndrome of asthenia and hypotension It is extremely difficult to ascertain whether the fall of blood pressure observed in hypertensive animals is due to a lack of a specific substance of the gland or to terminal phenomena dependent upon the poor general

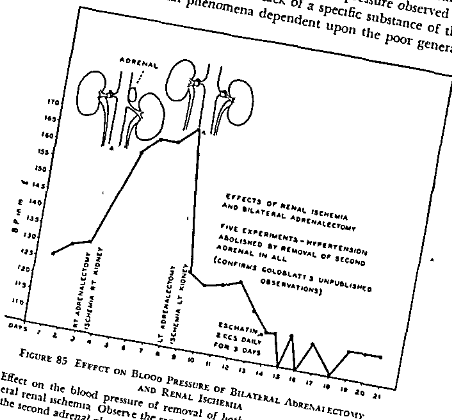


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Effect on the blood pressure of removal of both adrenals combined with bilateral renal ischemia Observe the rapid fall of blood pressure following removal of the second adrenal gland (After Blalock and Levy, Ann Surg, 1937, *106*, 826)

condition of the animal Goldblatt (1937a) showed that constriction of the renal arteries in adrenalectomized dogs did not produce a rise of blood pressure If hypertension had been produced previously, removal of the adrenals resulted in a fall of pressure. The administration of sodium chloride with sodium bicarbonate or sodium citrate prolonged the life of the adrenalectomized animals but was not capa-

ble of allowing the development of hypertension or of preventin its fall if it was already established.

In adrenalectomized dogs treated with cortical extract, Goldblat (1937a) observed small but significant rises of blood pressure following constriction of the renal arteries. Blalock and Levy (1937) found that in five dogs made hypertensive by partial constriction of the

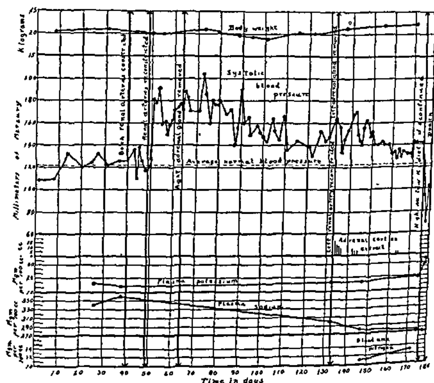


FIGURE 86 EFFECT OF REMOVAL OF BOTH ADRENALS ON HYPERTENSION FROM RENAL ISCHEMIA

Hypertension was first produced by constriction of both renal arteries; following this the adrenal glands were removed The left renal artery was reconstricted at the time that the left adrenal gland was removed (After Collins and Wood, Am J. Physiol, 1938, *123*, 224)

renal artery, removal of both adrenals was followed by a return of blood pressure to normal within 16 hours of removal of the second gland (figure 85)

Collins and Wood (1938) showed that adrenalectomy in hypertensive dogs led to a fall of blood pressure despite the administration

of cortical extracts and sodium chloride (figure 86). In some, however, the blood pressure remained slightly elevated despite the temporary omission of cortical extract. In adrenalectomized dogs treated with cortin, constriction of the renal arteries produced a rise of blood pressure, but the rise was only transient Similar results were obtained by Page (1938) who also observed that although the dose of cortical extract was increased as much as six times over that necessary to maintain life, renal ischemia produced only moderate rises of blood pressure in these animals. Rogoff, Nixon and Stewart (1940) found that in some hypertensive dogs subsequently adrenalectomized, hypertension was maintained for several days even though no substitution therapy was administered. From this they concluded that the adrenals play no essential rôle in this type of hypertension Subtotal adrenalectomy did not prevent the development of hypertension (Goldblatt, 1937a)

The rôle of the adrenals in renal hypertension has also been studied in the rat Díaz and Levy (1939) noted slight hypertrophy of the adrenal in rats made hypertensive by subtotal nephrectomy Removal of the adrenals in these animals produced a fall of blood pressure Dell'Oro (1942a, b) found that blood pressure fell to normal or subnormal values when the adrenals were extirpated in rats with hypertension produced by perinephritis The administration of desoxycorticosterone under these conditions produced a rise of blood pressure. Similar results were obtained by Gaudino (1944) (figure 87) who showed that bilateral adrenalectomy in white rats produced a progressive fall of blood pressure In some of the animals which survived, the hypertension returned at the end of several weeks due to the development of accessory adrenal glands which frequently are observed in rats of the breeding colony at the Institute of Physiology of Buenos Aires The administration of desoxycorticosterone at a time when the pressure was low caused it to return to normal levels Adrenalectomy in hypertensive rats produced a fall of blood pressure which in some animals spontaneously and gradually returned to hypertensive levels Desoxycorticosterone had no effect on the blood pressure of normal or hypertensive rats Braun-Menéndez and Foglia (1944) confirmed these changes in blood pressure after adrenalectomy and the lack of effect of desoxycorticosterone on the blood pressure of normal and hypertensive rats

From these various experiments it may be concluded that it has been well shown that removal of the adrenals prevents the develop-

ment or maintenance of hypertension of renal origin. In animals treated with cortical extracts it is possible to observe a certain degree of hypertension due to the substitution therapy which corrects in part at least the disturbances resulting from adrenalectomy As we have previously stated, it is difficult to judge up to what point the changes depend upon a specific action of the adrenals as opposed to the general changes resulting from adrenal dysfunction. Collins and Wood (1938) were of the opinion that the adrenal cortex is not concerned specifically with the etiology of hypertension, but that it

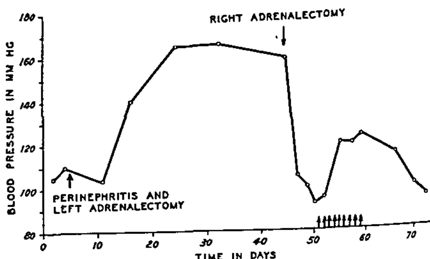


FIGURE 87 ACTION OF ADRENALECTOMY ON THE BLOOD PRESSURE OF A HYPERTENSIVE RAT

Blood pressure of a rat Removal of the second adrenal caused a rapid fall of blood pressure to preoperative levels. The administration of desoxycorticosterone acetate for nine days (arrows) produced a slight rise of pressure without, however, a return to the previous hypertensive level (After Gaudino, Rev Soc argent de biol, 1944, *20*, 460).

is important for the maintenance of blood pressure in normal and hypertensive animals.

The mechanism of action of the adrenals has as yet not been elucidated The following evidence indicates that the presence of the gland is not necessary for the renal pressor substance to exert its action. Fasciolo (1938b) found that kidney grafts from hypertensive dogs with renal ischemia produced a rise of blood pressure in recently adrenalectomized dogs. Enger, Linder and Sarre (1938b) showed that acute renal ischemia was capable of producing a rise of blood pressure

also explain in part the lack of hypertension in adrenalectomized animals with partial constriction of the renal artery. At the present stage of our knowledge, it can not be stated whether other factors are concerned in this action.

The reduced pressor action of renin in animals in adrenal insufficiency may be explained, according to Houssay and Dexter (1942), by the fall in the concentration of hypertensinogen in the blood and, in the terminal state of adrenal insufficiency, by a loss of vascular reactivity to hypertensin The diminution of hypertensinogen has also been observed by Lewis and Goldblatt (1942), and recently by Gaudino (1944). The administration of cortical extracts or desoxycorticosterone causes the concentration of hypertensinogen to return to normal This point has been discussed in greater detail in Chapter V.

HYPOPHYSIS AND HYPERTENSION. *Anterior Lobe.*—In normal dogs, removal of the hypophysis produces a fall of blood pressure as Braun-Menéndez observed in 1934. This was subsequently confirmed by Page and Sweet (1936, 1937) and by Goldblatt, Braden, Kahn and Hoyt (1942) Williams, Díaz, Burch and Harrison (1939) also observed a fall of blood pressure in hypophysectomized rats. The fall of pressure produced by complete hypophysectomy is due to the removal of the anterior lobe since extirpation of the posterior lobe or lesions in the region of the tuber do not greatly modify blood pressure in the dog (Braun-Menéndez, 1934).

In dogs made hypertensive by partial constriction of the renal artery, Page and Sweet (1937) observed that hypophysectomy caused the blood pressure to fall In some animals the blood pressure remained slightly elevated while in others it became entirely normal or fell below the normal level. When the pressure had fallen as a result of hypophysectomy, a new rise of pressure was obtained by further constriction of the renal arteries In some cases this rise was transitory and in some permanent. We have also observed a fall of blood pressure produced by complete hypophysectomy in two hypertensive dogs (unpublished results).

Constriction of the renal artery in hypophysectomized dogs produces a rise of blood pressure (Page and Sweet, 1937; Houssay and Fasciolo, 1938; Fasciolo, 1939; Goldblatt, Braden, Kahn and Hoyt, 1942) In acute experiments, Enger, Linder and Sarre (1938b) ob-

renal arteries in rats with diabetes *insipidus* produced the same elevation of blood pressure as in the control animals.

Sattler and Ingram (1941), in a group of hypertensive dogs, sectioned the supraoptico-hypophyseal tract in the median eminence, which functionally suppresses the posterior lobe. They obtained a fall of blood pressure in five of eight animals. These results were not entirely conclusive because the hypertension in the animals was only moderate

Frankel and Wakerlin (1943) observed that the excretion of the antidiuretic principle during normal hydration or dehydration was not modified by the production of renal hypertension in dogs

We may conclude, therefore, that the hypophysis is capable of altering renal hypertension without, however, being essential for its production or maintenance The anterior lobe is in all probability responsible for the changes observed, since it has not been shown that the posterior lobe particularly alters this hypertension. Removal of the anterior lobe of the pituitary produces important changes in other endocrine glands, and its rôle in hypertension may well be secondary to these glandular changes. If this is the case, therapeutic substitutes compensating for these deficiencies should restore the blood pressure which has fallen as a result of hypophysectomy. Page and Sweet (1937) believed in this hypothesis but were unable to obtain rises of blood pressure from the administration of folliculin or antuitrin The administration of thyroid extract by mouth produced a slight rise of pressure. Leathem and Drill (1944) observed that the amount of desoxycorticosterone necessary to maintain the blood pressure of adrenalectomized rats was only doubtfully effective in hypophysectomized rats. Large doses of adrenal cortical extract were partially effective but failed to maintain or restore normal levels Growth hormone did not prevent the fall of blood pressure immediately after hypophysectomy. In studying the effect of hypophysectomy on the blood pressure of rats, Braun-Menéndez and Foglia (1944) concluded that the fall of blood pressure was due to adrenal insufficiency as a result of adrenal atrophy. Anderson, Page, Li and Ogden (1944) reported that purified adrenocorticotropic hormone restored renal hypertension to the level present before hypophysectomy, whereas pure lactogenic hormone had no such effect We must conclude, therefore, that the mechanism of action of the hypophysis in hypertension is presumably in-

hypertensive rats the pressure fell from an average of 174 mm Hg to 103 mm Hg After delivery the pressure returned to a higher level. Page, Patton and Ogden (1941) showed that pseudopregnancy with deciduomas in hypertensive rats produced a fall of pressure similar to that observed during pregnancy and suggested, as Foà and collaborators had done, that the cause of the fall of pressure depended upon an endocrine factor

From these experimental data, it can be concluded that pregnancy has little or no effect on the pressure of normal animals but produces within the days preceding delivery a more or less marked fall of pressure in animals made hypertensive by renal ischemia, and that the pressure becomes elevated again after delivery In order to explain these findings, several hypotheses have been proposed

(1) A compensatory action of fetal kidneys was proposed by Grollman, Harrison and Williams (1940c), and accepted by Goldblatt for explaining the fall of pressure The experiments of Page, Patton and Ogden (1941), who observed the depressor effect to take place in the presence of deciduomas alone, if confirmed, make this hypothesis untenable

(2) Endocrine changes occurring during gestation may be the cause of the fall of pressure. Page, Patton and Ogden (1941) and Foà, Foà and Peet (1942) are proponents of this hypothesis It must be borne in mind, however, that definite proofs of this theory are still lacking Furthermore, Dill and Isenhour (1940) were unable to obtain changes of pressure of hypertensive rabbits by the administration of several hormone preparations

(3) Finally, there is the possibility that the placenta, introduced into the circulatory system, constitutes a shunt of less resistance analogous to that established by arteriovenous aneurysms This would explain the diminution of pressure in pregnancy by simple hemodynamic changes (Burwell, 1938) This concept should be put to experimental proof Ogden, Hildebrand and Page (1940) obtained a rise of pressure by constriction of the aorta below the origin of the renal arteries in five pregnant dogs and one pregnant cat The rise of pressure obtained was not very marked and disappeared at times immediately on release of the aortic constriction. These changes of ...ure were possibly the result of hemodynamic changes exclusively ... not of ischemia of the uterus

EFFECT OF PREGNANCY ON BLOOD PRESSURE OF HYPERTENSIVE ANIMALS. *Dogs*.—Mason, Harrison and Blalock (quoted by Dawson, Cressman and Blalock, 1941) observed that pregnancy in dogs with hypertension from renal ischemia produced a temporary fall of blood pressure without symptoms of uremia or eclampsia. Similar observations were made by Goldblatt (quoted by Dawson, Cressman and Blalock, 1941), Page (quoted by Page, Patton and Ogden, 1941), and Rodbard and Katz (1944). Erickson (1942) studied the variations of blood pressure of normal dogs and hypertensive dogs during pregnancy and came to the conclusion that the pressure falls during the latter part of pregnancy and persists at a low level for some days after parturition.

Rabbits.—Page and Ogden (1939) found no difference in the level of blood pressure of normal and pregnant rabbits. Corbit (1941) studied the fluctuations of blood pressure, blood urea nitrogen and urinary excretion of proteins during pregnancy in normal rabbits and rabbits made hypertensive by renal ischemia. In both groups of animals, pregnancy produced approximately a 20 per cent fall of blood pressure some days before delivery, the pressure returning to its initial level one to three weeks after parturition. Only in the hypertensives did he observe a slight fall in the level of blood urea nitrogen and a tendency to proteinuria. The author believed that the degree of fall of pressure was proportional to the number of fetuses present. Dill, Isenhour, Cadden and Kuder (1941) studied the effect of repeated pregnancies on rabbits with renal hypertension and observed no particular change of pressure. The method used by these authors for taking the pressure, however, was not reliable. They drew attention to the frequency with which fetal reabsorption and fetal death were observed in hypertensive rabbits. Nieva (1941) was unable to obtain pregnancy in a small number of hypertensive rabbits despite copulation on various occasions with different males.

Rats.—Grollman, Harrison and Williams (1940c) observed in rats made hypertensive by subtotal nephrectomy (method of Chanutin and Ferris, 1932) a fall of blood pressure during the last days of pregnancy which they attributed to the presence of fetal kidneys. They also observed that pregnant rats were less sensitive than normal to the pressor action of renin. Foà, Foà and Peet (1942) did not observe falls of pressure during pregnancy in normal rats but in

hypertensive rats the pressure fell from an average of 174 mm Hg to 103 mm Hg After delivery the pressure returned to a higher level. Page, Patton and Ogden (1941) showed that pseudopregnancy with deciduomas in hypertensive rats produced a fall of pressure similar to that observed during pregnancy and suggested, as Foà and collaborators had done, that the cause of the fall of pressure depended upon an endocrine factor.

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EFFECTS OF RENAL ISCHEMIA IN PREGNANT ANIMALS

Since it is hard to determine quantitatively the degree of renal ischemia produced by any of the usual methods, it is extremely difficult to come to definite conclusions concerning the greater or lesser sensitivity of pregnant animals to the hypertensive action of renal ischemia.

Some authors believe that pregnant animals are less sensitive to the pressor action of renal ischemia (Page, Patton and Ogden, 1941, in rats and rabbits; Dill, Isenhour and Cadden, 1939, in rabbits). Others have found no great difference from the normal (Dawson, Cressman and Blalock, 1941), while Dill and Erickson (1941) believed that pregnant rabbits are more sensitive than normal to renal ischemia. These latter authors (1938) observed eclamptic syndromes in pregnant dogs and rabbits. Renal ischemia, produced 2 to 30 days before the expected date of parturition, was followed by progressive asthenia, convulsions and coma, hypertension, hematuria and nitrogen retention Delivery or abortion was followed by rapid improvement None of the control animals developed this picture. At autopsy hepatic and renal lesions were found. Dawson, Cressman and Blalock (1941), in a careful study performed on 31 dogs, were unable to confirm the results of Dill and Erickson. They attributed the results of Dill and Erickson to a too marked constriction of the renal arteries. Dawson, Cressman and Blalock performed their experiments on animals during an advanced stage of pregnancy and, as has already been pointed out, the blood pressure tends to fall in the prepartal period. In order to obtain a given rise of blood pressure, therefore, it is probable that a greater degree of ischemia would have to be produced, which might well cause uremic symptoms and death. The number of abortions observed by Dawson and his collaborators in their operated dogs was considerable. It is not known, however, whether or not a procedure similar to the production of renal ischemia causes an equal number of abortions.

The experiments of Dill and Erickson (1938) would at first glance appear to open a new field in the study of the mechanism of eclampsia Since their observations have not been confirmed by others and since the syndrome described by them suggests a simple convulsive uremia due to an excessive constriction of the renal arteries such as one frequently observes in nonpregnant animals, their significance without further support is slight

TOXEMIA OF PREGNANCY AND ECLAMPSIA A number of investigations have been performed on the renal function of women with toxemia of pregnancy and eclampsia (Chesley, Connell, Chesley, Katz and Glisson, 1940; Wellen, Welsh, Taylor, and Rosenthal, 1942; Dill, Isenhour, Cadden and Schaffer, 1942, Kariher and George, 1943). The principal difficulty encountered in this type of study is the classification of the disease. It is difficult to determine clinically the degree of severity of the toxemia Corcoran and Page (1941d) and Wellen, Welsh, Taylor and Rosenthal (1942) found in some of their cases a diminution of the filtration fraction, $\frac{C_I}{C_D}$, and Lamport (1942), applying his formula to the data in the literature (1941) for calculating afferent and efferent arteriolar resistance in human kidneys, concluded that in toxemia of pregnancy there is a diminished filtration fraction. Since in this disease there is a reduction of plasma protein and an increase of blood pressure, both of which might produce an increase of filtration fraction (Lamport, Maculla and Graff, 1943), Lamport concluded that the diminution of the ratio, $\frac{C_I}{C_D}$, was due to a specific effect of the toxemia which might well be on the basis of thickening of the basement membrane of the glomerulus

There is no doubt but that eclampsia or toxemia of pregnancy represents a vascular syndrome with certain aspects which suggest that the kidney is involved in the process Bell (1932) showed that the basement membrane of the glomerular capillaries was thickened in fatal cases of eclampsia This was confirmed by several investigators (Baird and Dunn, 1933; Wilbur, 1931; Weiss, Dexter, Parker and Tenney, 1940) Page and Cox (1938) found similar lesions in some normal women which suggested that this lesion was not specific for eclampsia Weiss, Dexter, Parker and Tenney (1940) also found degenerative lesions in the cells of the convoluted tubules in eclampsia and considered that the renal lesions were a type of glomerulonephrosis These investigators believed that toxemia of pregnancy could produce a permanent hypertension secondary to the renal lesions, but that the primary factor of toxemia probably originated in the placenta Up to the present, however, no pressor substances have been found in the placenta (Haynes, Dexter and Weiss, unpublished, and Nieva, unpublished). Substances with a

renin-like action have not been found in the placenta (Dexter and Weiss, 1941; Nieva, unpublished) Dexter and Haynes (1944), however, reported the presence of appreciable amounts of renin in the systemic blood of 3 patients with severe toxemia of pregnancy

In summary, therefore, it may be concluded that pregnancy causes a fall of blood pressure in the latter part of pregnancy in the majority of animals with experimental renal hypertension The mechanism of this fall has as yet not been elucidated.

Constriction of the renal artery during pregnancy apparently does not prevent the appearance of hypertension or alter the course of pregnancy The complications observed by some investigators are probably related to the appearance of renal insufficiency or perhaps are due to surgical trauma.

Removal of the adrenal medulla does not modify the course of hypertension of renal origin. Bilateral adrenalectomy prevents the development and maintenance of hypertension even though cortical extracts are administered The concentration of hypertensinogen is reduced in adrenalectomized animals and the vascular reactivity is diminished only in the terminal stages of adrenal insufficiency.

Removal of the anterior lobe of the hypophysis produces a fall of pressure in animals with renal hypertension The effect may be transitory. Renal ischemia produces hypertension in hypophysectomized animals The posterior lobe of the pituitary does not appear to play any important rôle Removal of the thyroid, parathyroid, testicles and ovaries does not prevent the development of hypertension from renal ischemia

Pregnancy has little if any effect on the blood pressure of normal dogs. In animals with experimental hypertension, a fall of blood pressure has been observed in the latter part of pregnancy. The mechanism of this fall has not as yet been elucidated

Constriction of the renal artery during pregnancy does not prevent the appearance of hypertension nor does it apparently modify the course of pregnancy The complications observed by some investigators are probably related to the appearance of renal insufficiency or perhaps to surgical trauma.

In eclampsia in pregnant women, renal lesions consisting of thickening of the basement membrane of the glomerulus have been de-

CHAPTER XI

OTHER VASOCONSTRICTOR AND PRESSOR SUBSTANCES

A group of substances will be discussed in this chapter, some of which have not been well identified. Their recognition is important, however, for the following reasons: (a) They have been thought to be responsible for the production of hypertension; (b) they have been considered to play a certain rôle in the production of hypertension; (c) they have created difficulties in the recognition of specific vasoconstrictor substances contained in blood; (d) they possess certain similarities to the substance possibly responsible for hypertension, hypertensin

TYRAMINE

Since tyramine has long been known to have a pressor action, a number of studies have been performed with the object of ascertaining if it plays some rôle in hypertension. The chemical determination of this substance in blood has been performed in the majority of cases by using the reaction of Gerngross, Voss and Herfeld (1933), by which a red color is produced by 1-2 nitrosonaphthol and nitric acid. This reaction is positive for para substituted phenols which contain an H in the ortho position. By extraction with amyl alcohol and a solution of sodium carbonate, tyramine may be separated from other phenols

Heinsen and Wolf (1934, 1935a, b) investigated the tyramine content of blood using amounts varying between 150 and 400 cc. The reaction was negative in essential hypertension and in normal subjects, but they obtained positive reactions in patients with chronic hypertensive nephritis and malignant nephrosclerosis The authors concluded that tyramine plays an important etiologic rôle in so-called "pale" hypertension.

Using a different method, Mande (1941) concluded that tyramine ... nephritis ... en the

amount of tyramine and the blood pressure. Enger and Arnold (1936), on the other hand, showed that the reaction of 1-2 nitrosonaphthol was negative in the blood of normal subjects and those with essential hypertension, amyloid nephrosis and acute nephritis. In chronic nephritis with hypertension and in malignant nephrosclerosis, their results were positive, doubtful, or negative in different cases Later, in 1937, the same investigators modified the method of Heinsen and Wolf so that they were able to detect 20 gamma of tyramine in 300 cc of blood This increased the sensitivity of the original method some three times In nephritis and in the majority of cases of malignant nephrosclerosis they obtained negative results They therefore concluded that there was no evidence that tyramine was an important etiologic factor in hypertension of renal origin

Similar results were obtained with a different method by Schuler, Bernhardt and Reindel (1936) Govaerts (1937), using the reaction of Gerngross and collaborators, on extracts of five cc. of serum and cerebrospinal fluid, were likewise unable to obtain positive reactions in patients with nephritis and hypertension.

Experimental attempts have been made to clarify the rôle of tyramine in the production of hypertension. Wolf and Heinsen (1935) observed that ligation of branches of the renal artery produced rises of blood pressure in dogs The "tyramine" reaction became positive after operation Loeper, Lemaire and Cottet (1938) made similar observations on rabbits following ligation of the ureters Govaerts (1937), however, obtained negative results with the blood of dogs with hypertension from renal ischemia Robbers and Westenhoeffer (1939) investigated this problem with a pharmacologic approach They studied the effects of cocaine which is known to abolish the action of tyramine (see Burn and Tainter, 1931) on hypertension produced by ligation of a renal artery In none of eight dogs studied did they observe a fall of pressure from cocaine, from which they concluded justifiably that tyramine was not the agent responsible for the hypertension in these animals

Attempts have been made to produce persistent elevation of blood pressure by the continuous injection of tyramine. Robbers (1936) injected tyramine intravenously into cats and dogs in doses of 0 05 to 0 4 mgm per kgm per minute, observing that after some 45 minutes the pressor effect disappeared The blood pressure remained low although the injection was continued. Death supervened from

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Using a different method, Mande (1941) concluded that tyramine was regularly increased in the blood of patients with chronic nephritis and hypertension. No parallelism, however, was found between the

800 hypertensives in which guanidine was measured by the method of Major and Weber (1927). In 625 patients with hypertension and a nonprotein nitrogen level of 40 mgm per cent or less, only 200 showed increases while 425 had normal values In hypertension with nitrogen retention, however, an elevation of "guanidine" was found with considerable frequency

Since guanidine is a substance with a pressor action, its presence in patients with renal disease suggested the possibility that it might play some rôle in the hypertension associated with nephritis The reactions employed for the measurement of guanidine, however, are not specific Increases of "guanidine" found may possibly have been due to substances of similar chemical structure but devoid of pressor activity In this regard, Major (1929) found that while guanidine and methylguanidine were pressor substances, other similar compounds were inert or even depressor

An increase of "guanidine" has been found in a number of diseases such as cirrhosis, tetany, dehydration, and so forth, in which the blood pressure is normal (Turriès, 1933, Dodd and Minot, 1934, Andes, Andes and Myers, 1937, and others) It appears improbable, therefore, that "guanidine" plays a fundamental rôle in hypertension Experiments on animals support this conclusion Goldblatt, Lynch, Hanzal and Summerville (1934) and Helmer and Page (1938) found no increase of "guanidine" in the blood of hypertensive dogs if renal function was normal Major, Weber and Rumold (1939) observed that increases of "guanidine" in the blood of dogs with renal insufficiency occurred with or without a concomitant hypertension According to them, the substance measured might well be a derivative of guanidine such as glycocyamidine

VASOACTIVE SUBSTANCES IN EXTRAVASATED BLOOD[1]

Aside from the possible presence of such substances as adrenalin and pitressin originating in the glands of internal secretion, and of tyramine, guanidine and even histamine, which are substances with a powerful pharmacologic action possibly existing in normal blood, other substances have been described, the chemical constitution and physiologic significance of which have not as yet been elucidated.

O'Connor (1912) showed that there was a vasoconstrictor substance

[1] Gaddum (1936)

circulatory collapse in the course of six to eight hours Wolf and Ludolf (1937) confirmed the findings of Robbers but used smaller doses in the neighborhood of 0 002 mgm. per kgm per minute The pressure rose slowly and the effect was more prolonged. Two to three hours afterwards, however, the animals died in respiratory paralysis

Histological changes produced by the injection of tyramine for prolonged periods have been studied by Duff, Hamilton and Magner (1939) in rabbits They gave daily injections of 50 to 100 mgm of tyramine intravenously over the course of 1 to 106 days and observed arterial and arteriolar lesions consisting of hyaline degeneration and necrosis. Enger and Lampas (1940) also observed renal changes and changes in the arteries of dogs treated for more than two years with tyramine The clinical picture and anatomical changes observed were different from those of "pale" hypertension

In summary it may be said that the rôle of tyramine in hypertension of renal origin does not appear to be very important It has not been shown that there is an increase of this substance in renal hypertension Color reactions for tyramine have little specificity and may well reflect the presence of similar substances devoid of pressor action.

GUANIDINE

Ditman and Welker (1909) attributed hypertension and the symptoms of nephritis, eclampsia, and so forth, to the retention of several products (creatinine, methylguanidine and guanidine) derived from a defective metabolism of creatine. This belief was subsequently reiterated by Boyd (1916). Major and Weber (1927) improved the methods of detection of guanidine in the blood and, in a group of hypertensives, found a slight increase of "guanidine" in essential hypertension and a definite increase in those with renal hypertension. Similar results were obtained by Bohn and Schlapp (1932) who observed an increase of "guanidine" in "pale" hypertensives, and normal values in "red" hypertensives

Pfiffner and Myers (1930) and deWesselow and Griffiths (1932) also demonstrated an increase of "guanidine" in the blood in certain cases of hypertension

Kleeberg and Schlapp (1930), Marcolongo (1933) and Andes, Linegar and Myers (1937) were of the opinion that the increase of "guanidine" was related more to the state of excretory renal function than to the height of the blood pressure. Major (1938) studied

blood was attributed by Freund to the presence of *Spätgift.* This produced vasoconstriction, contraction of the isolated intestine of mammals and contraction of the uterus

In summary, therefore, blood extracted from the body can acquire diverse pharmacologic properties which appear after coagulation (Simon, 1938, Simon and Komlos, 1938), agitation of heparinized blood, or even simple standing (Phemister and Handy, 1927; Landis, Wood and Guerrant, 1943; Landis, 1944) These properties are probably due to the presence of several substances Adenylic acid appears to be the cause of the inhibition of intestinal contractions and of the vasodilator action which appears in the early period following removal of the blood The actions attributed to *Spatgift* possibly are due to the presence of more than one substance still unidentified

Before attributing a specific rôle to the vasoconstrictor action which appears in blood under experimental and pathologic conditions, it is necessary to demonstrate that such action is not due to the presence of nonspecific substances such as vasoconstrictin or *Spatgift* Many errors of interpretation have been committed by not considering this possibility as Landis (1944) has emphasized Landis made an extensive study of the technique by which the constrictor action of shed blood may be avoided when tested on the isolated rabbit's ear To arrest coagulation from the beginning, the donor rabbit, which supplied the blood used for perfusion, was given a large intravenous dose of heparin 15 to 30 minutes before blood was withdrawn from the heart Such "preheparinized" blood, coupled with painstaking removal from glassware and syringes of all chemical residues of previous perfusions, withdrawal of blood into a syringe containing an excess of heparin, and centrifugation of blood in plastic tubes, resulted in the maintenance of a constant perfusion rate at constant, low mean pressure.

SUBSTANCES PRODUCED BY AUTOLYSIS OR DIGESTION OF THE KIDNEY

Hartwich and Hessel (1932) observed that a pressor substance other than renin was formed by autolysis of kidneys over the course of several weeks at 37°C This substance had a more rapid and shorter action than renin It was soluble in organic solvents and was ultrafilterable They believed it to be an amine which was formed in the kidneys as a result of autolysis but they did not identify it.

in serum which was liberated by platelets when the blood coagulated It was considered that it had a beneficial action in producing hemostasis in wounds by producing local vasoconstriction and preventing blood loss from the wound. The vasoconstrictor action of defibrinated blood is due to this substance which some authors have called *vasotonin* or *vasoconstrictin*. The vasoconstrictor action of defibrinated blood can be prevented by circulating the blood through the lungs,[2] the liver (Bornstein, 1926; Bing, 1941b), or the spleen (Bing, 1941b) The kidney (Bayliss and Ogden, 1933, Bing, 1941b) and the placenta (Budelmann, 1929) do not diminish its vasoconstrictor action Ergotoxin abolishes the action of vasoconstrictin (Heymans, Bouckaert and Moraes, 1932a, b; Bayliss and Ogden, 1933, Bing, 1941b) and the same is true of 0.01 M potassium cyanide (Euler and Sjostrand, 1941b).

As regards the pharmacology of the substance producing the vasoconstrictor action of serum, there is no agreement among investigators. It has been reported to have a stimulating action on the isolated heart of batrachians (Clark, 1913), on the isolated auricle of the rabbit (Clark, 1913) and on the intestine and uterus of rabbits and guinea pigs (O'Connor, 1912). Vasodilator and depressor actions have been described together with an inhibiting action on the contractions of the isolated intestine. These apparent contradictions were clarified by the investigations of Freund (1920a, b, 1921) who found that the pharmacologic properties of blood depended upon the time transpiring after its extraction and coagulation. This investigator observed that platelets liberated two substances with a different action which he called *Frühgift* and *Spätgift*. The former appeared immediately after destruction of the platelets and produced vasodilatation, inhibition of the contractions of the isolated intestine of the rabbit and contraction of the cat uterus Studer, Fleish and Croisier (1938) described another vasodilator substance which was produced by lysis of red cells and which was identical with adenosintriphosphoric acid. The investigations of Zipf (1930, 1931a, b) and of Barsoum and Gaddum (1935) appeared to show that *Fruhgift* was identical with adenylic acid. *Fruhgift* disappeared after a few minutes due to the presence of enzymes in blood which destroyed adenylic acid. The appearance of other properties in shed

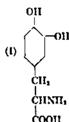
[2] Starling and Verney (1925); Bayliss and Ogden (1933), Eichholtz and Verney (1924), Herrick and Markowitz (1929); Hemingway (1931), Braun-Menéndez and Fasciolo 1939a)

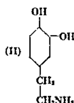
tyrosine with renal tissue but not with liver tissue. With phenylethylamine as the substrate, they did not obtain tyramine Better yields were obtained by incubating under low oxygen pressure. It should be pointed out that they used a method for the measurement of tyramine which has not been well studied. This method (Schuler and Widermann, 1935) consisted of incubating the solution with kidney slices In this way tyramine was oxidized to adrenalin which was then measured by Folin's reaction The formation of tyramine from tyrosine in the kidney was not observed by Heinsen (1937) who used the reaction of Gerngross for the detection of tyramine

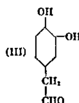
Werle and Mennicken (1937), using dialyzed extracts of kidneys, noted the formation of pressor substances derived from tyrosine and tryptophane. These substances, which the authors supposed were tyramine and tryptamine, respectively, were not formed in the presence of cyanide nor from extracts of liver, spleen, lung or pancreas, nor from extracts of chicken, horse, goat, hog or monkey kidneys The only active renal extracts obtained were those of guinea pigs and rabbits The authors excluded the possibility of bacterial action

Holtz (1937, 1938) and Holtz and Janisch (1937) confirmed the formation of pressor substances from tyrosine in renal extracts of guinea pigs and rabbits

ACTION ON DIOXYPHENYLALANINE. Holtz, Heise and Ludtke (1938) observed that by anaerobic incubation of renal extracts with dihydroxyphenylanine (I) (*dopa*), a pressor substance was formed by decarboxylation which they identified as hydroxytyramine







(II) The reaction was inhibited by cyanide Decarboxylase (Holtz, Credner and Walter, 1939) is found in livers and kidneys of guinea pigs, rabbits, pigs, sheep, goats and chickens, and in the intestine of

By incubating kidney tissue for 24 to 48 hours at 37°C, Victor, Steiner and Weeks (1940) obtained pressor substances, the concentration of which increased with time up to 48 hours. These substances were produced under anaerobic but not under aerobic conditions. These investigators excluded the possibility of bacterial action. They did not identify the substances produced.

Drill (1942) prepared extracts of autolyzed kidneys and succeeded in isolating isoamylamine and tyramine. Part of the pressor action was due to the presence of phenylethylamine. These substances had been isolated by Barger and Walpole (1909) from putrified muscle. Abelous, Ribault, Soulié and Tougan (1906) had also observed the formation of pressor substances in putrified muscles.

Williams, Harrison and Mason (1938) obtained similar substances by the digestion of saline extracts of kidneys incubated with pancreatin at 37°C. for 12 to 16 hours without maintaining aseptic precautions. In order to separate the depressor substances, they extracted the active substance with acetone and washed the solution with ether. The substance resisted boiling. Its pressor action was similar to that of tyramine in that it was abolished by cocaine. They obtained pressor substances by digesting extracts of hog liver, spleen, lung and serum and also of milk and white beans with pancreatin. Results were negative with extracts of heart, peas, sweet potato, gelatin and egg white.

According to Williams and Grossman (1938) there were two pressor substances in the perfusion fluid of kidneys, renin and another which was similar to adrenalin in that it was thermostable and soluble in 85 per cent alcohol. If kidneys were removed two hours previously, the action was more intense. The pressor action was not observed when other organs such as spleen, lung and liver were used. It is possible that the thermostable substance was hypertensin.

FORMATION OF PRESSOR AMINES BY THE KIDNEY

It is possible that the kidney elevates blood pressure through mechanisms other than the secretion of renin. Actually it has been shown that renal tissue is capable of forming pressor amines but their physiologic importance still remains to be demonstrated.

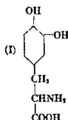
FORMATION OF TYRAMINE. According to Schuler, Bernhardt and Reindel (1936), tyramine can be produced by the *incubation of*

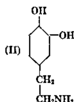
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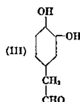
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guinea pigs but not in the intestines of other animals.

Under aerobic conditions dihydroxytyramine is rapidly oxidized by the action of amine oxidase to dioxyphenylacetaldehyde (III) which is a depressor substance. The extracts were prepared by extracting minced kidneys with phosphate buffer at pH 7.4. Incubations were made for eight hours at 39° C. in the presence of toluol. (Bing 1941a) repeated and confirmed the experiments of Holz and his collaborators. In addition, perfused kidneys with dioxyphenylalanine and observed that a pressor substance was produced The less the amount of blood perfused through the kidney, the greater was the amount of pressor substance formed. The liver and intestine, perfused with blood containing dioxyphenylalanine under the same conditions of ischemia, did not form pressor substances

Bing and Zucher (1941b) obtained a pressor substance by incubation of renal extracts from guinea pigs but not from cats with phenylalanine and with dioxyphenylalanine In addition, they showed that human kidneys also contained the enzymatic system necessary for the transformation of *dopa* into a pressor substance Analogous results were also obtained by perfusion The possibility that renin was the decarboxylating enzyme was at first entertained, but experiments demonstrated that renin was not capable of accelerating the reaction This was confirmed by Croxatto and Croxatto (1942c). Blaschko (1942) also obtained the formation of hydroxytyramine from *dopa* with extracts of mammalian kidneys.

Bing and Zucker (1941a) tried to demonstrate the importance of the reaction dioxyphenylalanine-hydroxytyramine in hypertension from renal ischemia They injected *dopa* into totally ischemic kidneys and observed that on re-establishing the circulation two to three hours later a rise of blood pressure ensued. The kidneys injected with *dopa* produced a rise of pressure when the circulation was re-established after four to five hours but not after two to three hours The authors did not conclude from these experiments that the mechanism of hypertension from renal ischemia was on this basis They mentioned the possibility only that decarboxylation of *dopa* represents an example of a type of reaction which can occur in the ischemic kidney During ischemia, decarboxylation predominates over oxidation of certain amino acids and pressor substances are thus formed.

In favor of this hypothesis might be mentioned the work of Oster

PRESSOR SUBSTANCES FORMED IN OTHER ORGANS

Collip (1928a, b) prepared pressor extracts from several tissue (muscle, liver, kidney, spleen, ovary, testicle, stomach and intestine) These tissues were extracted with boiling water. After concentration the extract was extracted with acetone. Using commercial prepara tions of pepsin and pancreatin, active extracts were also obtained Extracts of prostate gave a pressor effect which was attributed to a different substance.

Some properties of the substance were as follows: It did not alter the blood sugar; the pressor action was increased by small doses of ergotamine while larger doses produced an inversion of its pressor effect; cocaine acted as an antagonist; atropine did not modify it; nicotine increased it, in high concentration it inhibited the isolated intestine, uterus and heart, it did not produce tachyphylaxis.

Page (1935b, 1937) described pressor effects from ventricular fluid of man and other animals This action was mediated by the nervous system. None of these pressor substances has been accurately identified

PEPSITENSIN

FORMATION Croxatto and Croxatto (1942a) observed that a pressor substance with properties similar to those of hypertensin was formed by incubating pepsin with hypertensinogen This substance was called pepsitensin

The procedure of preparation was as follows (Alonso, 1942): Hypertensinogen was acidified to pH 3.5. One-tenth per cent commercial pepsin (Parke, Davis and Company) was added and the mixture was left for 3 to 5 hours at 38°C. It was neutralized and 3 volumes of alcohol added. The filtrate was concentrated *in vacuo* and extracted with ether. The aqueous phase was dialyzed in cellophane sacs Pepsitensin crossed the cellophane and the solution could then be concentrated.

The reaction also took place at higher pH's but not above a pH of 7 (Croxatto and Croxatto, 1942a; Helmer and Page, 1942)

Using other substrates such as lactalbumin, lactoglobulin, casein, and ovalbumin, the same authors obtained the formation of pressor substances With gelatin as the substrate or trypsin in place of pepsin, no pressor substances were obtained.

Helmer and Page (1942) also obtained a pressor substance by using crystalline pepsin They used hypertensinogen prepared by precipitation with potassium phosphate, incubated it with pepsin at 40°C for 10 minutes, and then removed the proteins by boiling for 10 minutes.

According to Weber, Major and Lobb (1942), the maximal pressor action is obtained by incubating at pH 5 to 6 for 30 minutes These investigators did not obtain pressor substances with trypsin, cathepsin or takadiastase.

Quantitative studies on the formation of pepsitensin at different pH's and times of incubations have not as yet been done This is due to the difficulty of freeing pepsitensin from the depressor substances which accompany it. These depressor substances frequently mask the pressor action, and this undoubtedly accounts for the earlier negative results which were obtained by Braun-Menéndez, Fasciolo, Leloir and Muñoz (1940a) It has also been observed that the same lot of pepsitensin produces a pressor response in some animals and no pressor response in others

According to Alonso (1942) a similar product may be obtained by prolonged treatment with acid By incubating hypertensinogen with 5 N hydrochloric acid (3 5 per cent) and incubating for 6 days at 38°C, a pressor substance was obtained In five hours at pH 3.1, a pressor substance was likewise obtained although less in amount

PROPERTIES Pepsitensin has chemical and pharmacologic properties similar to those of hypertensin Alonso (1942) and Alonso, Croxatto and Croxatto (1943) mentioned the following characteristics common to both substances It does not produce tachyphylaxis, adrenalectomy and nephrectomy do not influence the pressor action, the previous injection of Fourneau 933 does not invert its pressor properties, the pressor action is potentiated by veritol and atropine does not modify it; it stimulates the musculature of intestine, uterus and urinary bladder of rats and cats and this action is not abolished by atropine, it is thermostable but is destroyed in 15 minutes at 100°C in 0 15 N sodium hydroxide, it loses its action by incubation with preparations of trypsin, tyrosinase, amine oxidase and renal hypertensinase, incubation with crystalline pepsin also inactivates it Its solubility in glacial acetic acid and alcohol and its insolubility in ether and amyl alcohol are the same as for hypertensin. Pepsitensin

is precipitated with phosphotungstic acid but not with trichloracetic acid.

In contrast with these many similar properties, Braun-Menéndez, Fasciolo, Leloir, Muñoz and Taquini (1943) observed that both substances differed in their resistance to hypertensinase from red blood cells of dogs While hypertensin was destroyed rapidly, pepsitensin preserved its activity. This has been confirmed by Dexter, Haynes and Bridges (1944). Plentl and Page (1944c) found that

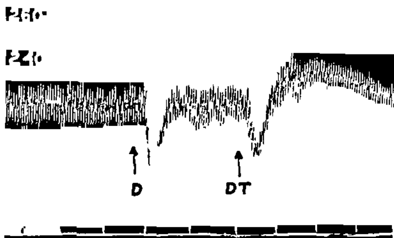


FIGURE 88 DESTRUCTION OF THE PRECURSOR OF PEPSITENSIN BY THE PREVIOUS ACTION OF RENIN

Rises of blood pressure in the dog produced by. (D) extract of plasma treated with renin, dialyzed, and then treated with pepsin (DT) extract of dialyzed plasma then treated with pepsin Blood pressure in mm Hg, time in minutes (After Braun-Menéndez, Fasciolo, Leloir, Muñoz and Taquini, Rev. Soc argent de biol, 1943, *19*, 304)

pepsitensin and hypertensin differed in respect to magnitude of proteolytic coefficients as well as hydrogen ion optima when incubated with varying amounts of crystalline pepsin.

RELATION BETWEEN HYPERTENSINOGEN AND PRECURSOR OF PEPSITENSIN. Hypertensinogen, after being left at a pH of 4 for 30 minutes at 25°C. or after precipitation with three volumes of alcohol and redissolved, does not produce hypertensin when treated with renin Pepsin, however, when incubated with

hypertensinogen treated in this manner is still capable of producing pepsitensin (figure 89) There is no doubt, therefore, that the substrate of renin and of pepsin is somewhat different. Pepsin appears to act on denatured hypertensinogen. It has been shown that while both substrates are different, the part of the molecule containing the pressor group is common for both Thus hypertensinogen

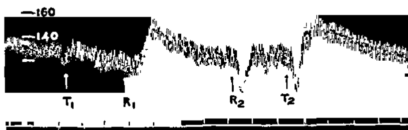


FIGURE 89 DESTRUCTION OF THE PRECURSOR OF PEPSITENSIN BY THE PREVIOUS ACTION OF RENIN

Rises of blood pressure in the dog produced by the injection of extracts soluble in 70 per cent alcohol from (T_1) untreated plasma (R_1) plasma treated with renin, (R_2) alcohol precipitate of R_1 redissolved and treated with pepsin (T_2) alcohol precipitate of (T_1) redissolved and treated with pepsin Blood pressure in mm Hg, time in minutes (After Braun-Menéndez, Fasciolo, Leloir, Muñoz and Taquini, Rev Soc argent de biol, 1943, *19*, 304)

treated with renin loses its capacity for forming pepsitensin when incubated with pepsin (figures 88 and 89) (Braun-Menéndez, Fasciolo, Leloir, Muñoz and Taquini, 1943)

It is possible that pressor substances other than that of the pressor system renin-hypertensinogen-hypertensin are concerned in arterial hypertension

An increase in the concentration of tyramine and guanidine in the blood has been observed in some cases of hypertension The methods used, however, are of doubtful specificity The increases observed also bear a closer relation to the degree of renal excretory insufficiency than to the degree of hypertension

Certain vasoactive substances, such as *Fruhgift, Spatgift,* vasoconstrictin, and so forth, which appear in shed blood have been dis-

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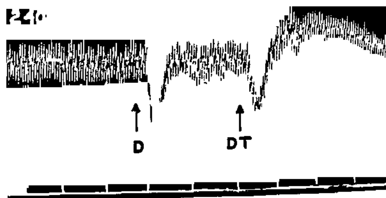


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cussed in this chapter. They are of importance mainly because they interfere with the identification of other vasoconstrictor substances in the blood of hypertensive animals and patients.

Studies have been made on the ability of the kidney *in vitro* to produce pressor substances other than renin. It appears that renal tissue can produce some pressor amines (tyramine, isoamylamine, phenylethylamine, hydroxytyramine, and so forth), but it is still not known what rôle these substances may play in the genesis of hypertension

A pressor substance, pepsitensin, similar to hypertensin is produced by the action of pepsin on hypertensinogen. Although this substance does not play any rôle in hypertension, it is of interest since it is the product of an enzymatic reaction, and its origin from hypertensinogen is the same as that of hypertensin. Pepsitensin and hypertensin may at this time be differentiated only by their behavior in regard to the hypertensinase of red blood corpuscles

CHAPTER XII

HUMAN HYPERTENSION

Our knowledge of hypertension has advanced in three different periods The first period began with Bright (1827, 1836) who associated cardiac hypertrophy observed in subjects with renal disease with a change in the blood capable of increasing the work of the heart or of affecting small vessels in such a manner as to create an obstruction to the passage of blood through the different subdivisions of the vascular tree His idea of the renal origin of this disorder found support in the anatomical studies of Toynbee (1846), who observed thickening of the walls and diminution of the calibre of the renal arteries, and in those of Kirkes (1855) who demonstrated a relationship between hypertension and arteriosclerosis

The second stage of our knowledge of hypertension began in 1880. At this time, von Basch introduced the sphygmomanometric method for measuring blood pressure in man This method came into general use a few years later when Riva Rocci used the pneumatic cuff for compressing the artery In 1893 von Basch published the results of his extensive experience and drew attention to the frequent absence of demonstrable signs of arteriosclerosis in patients affected with hypertension In this way, the disease which today is called essential hypertension, took origin and was subsequently studied in detail by Allbutt (1895), Huchard (1889), Janeway (1913a, b), and Volhard and Fahr (1914).

The lack of demonstrable renal lesions for many years after the onset and even throughout the entire course of the disease drew the attention of some investigators away from the renal origin of hypertension Numerous theories of etiology were evolved The discovery of the pressor action of extracts of the adrenal medulla (Oliver and Schaefer, 1895), and of its active principle, adrenalin (Takamine, 1901, and Aldrich, 1905), aroused the interest of many in regard to the relation of hypertension to this gland (Josué, 1903, Vaquez, 1904).

The presence of adrenalin in the blood of essential and nephritic hypertensives has not been demonstrated, however, even by using methods of extreme sensitivity (Hulse, 1922)

It was also thought that the cause of hypertension might be neurogenic in origin. Some authors, such as Monakow (1920) and Raab (1929, 1931) considered that hyperirritability of the vasomotor centers was of importance Kahler, in 1924, attributed hypertension to overactivity of the hypothalamic centers and proposed a theory of primary central origin. This theory was adopted with enthusiasm by Castex (1929) Against this theory, however, was the demonstration that the hypothalamic centers were not involved in the maintenance of normal blood pressure and that in its absence, reflexes regulating blood pressure were preserved. This theory also lacked pathologic confirmation (Braun-Menéndez, 1934; Leiter and Grinker, 1934)

The possibility of producing permanent hypertension by section of the depressor nerves (Koch and Mies, 1929) and the demonstration in hypertensive subject of changes in the responses of the carotid sinus to various stimuli, caused certain investigators to suggest that diminution in the sensitivity of the carotid sinus to physiologic stimuli produced changes in blood pressure and was, therefore, concerned in the genesis of hypertension (Mies, 1932, Heymans, Bouckaert and Regniers, 1933) The subsequent studies of Keele (1933) and of Gammon (1936), however, invalidated this hypothesis

During this period, extensive studies were made of this disease from a clinical point of view. Although different types of hypertension were recognized, concepts of etiology and pathogenesis were confused. It became increasingly apparent that many patients with essential hypertension developed some reduction of renal function and were difficult to differentiate from those with true primary renal disease. It also became apparent that hypertension was frequently associated with disorders of the kidney and of the urinary tract. In some clinics, the kidney was considered to be the cause of all or at least the majority of cases of human hypertension Among these was Volhard who studied this disease extensively from the clinical and anatomical viewpoint (Volhard and Fahr, 1914) and classified hypertensives in two major groups: the "red" and the "pale" (Volhard, 1923) He suggested a humoral origin for the vascular lesions appearing in the malignant stages of hypertension.

In 1934, Goldblatt introduced the third period in our knowledge of hypertension by reproducing benign and malignant hypertension experimentally. His studies, together with those of many others,

have established a relationship between the kidney and hypertension in man and opened new fields for the investigation of this important medical problem.

CLASSIFICATION OF HUMAN HYPERTENSION

Hypertension is a manifestation common to several diseases. The systolic pressure alone, or both systolic and diastolic pressures, may become elevated The former is found in patients with an increased systolic volume output of the heart such as occurs in aortic insufficiency, *arteriovenous aneurysm, auriculo-ventricular dissociation,* and so forth, and in those with loss of elasticity of the arteries such as is observed in some cases of advanced arteriosclerosis In these patients the symptomatology, clinical course and prognosis depend upon the underlying disease causing the hypertension

An elevation of both systolic and diastolic pressure, on the other hand, is associated with a clinical syndrome characterized by a certain group of circulatory manifestations In this syndrome, a generalized vascular sclerosis develops which eventually ends in cerebral, cardiac or renal complications.

Before the experimental studies of Goldblatt and collaborators in 1934, hypertension was classified according to its clinical course Two types were distinguished The first was benign hypertension with a generally favorable course which was characterized by an increase of blood pressure, signs of cardiac strain such as hypertrophy of the left ventricle and symptoms of insufficiency, and by the absence of renal insufficiency. The second was malignant hypertension characterized typically by vascular changes at an early age. Cerebral symptoms, changes in the eyegrounds, and renal insufficiency frequently appeared. These symptoms and signs led to an unfavorable prognosis within a short period of time Volhard (1923) divided hypertension into the "red" and "pale" types. The former was found in plethoric individuals of pycnic habitus. Examination revealed hypertension alone and no vascular, renal or eyeground changes The latter, according to Volhard, had a generalized vasoconstriction and as a result there were changes in the eyegrounds, cerebral symptoms and early renal insufficiency.

As a result of the experimental studies of recent years, classifications of hypertension have depended upon the presence or absence of demonstrable renal disease Fishberg (1939) divided hypertension

into two large groups, one in which the hypertension resulted from disorders of the kidney or of the renal vessels, and the other in which the hypertension was not of renal origin or in which the renal factor was at least not demonstrable. Williams and Harrison (1939) classified hypertension according to etiologic and predisposing factors Schroeder and Steele (1939) classified hypertension according to renal, endocrine, nervous and vascular factors. Weiss (1940), basing his classification on clinical and physiologic characteristics, divided hypertension into three general groups: (1) hypertension of vascular origin with renal ischemia; (2) hypertension of organic vascular origin without renal ischemia; and (3) hypertension of vascular non-organic origin in which were included endocrine and nervous disorders. Page (1939d) classified hypertensive disease in five large groups, four of known cause—renal, cerebral, cardiovascular, endocrine, *and a fifth of unknown cause in which essential and* malignant hypertension were included

In this monograph we will use the following classification which is based in part on preceding classifications but fundamentally on the experimental findings already discussed

A HYPERTENSION OF RENAL ORIGIN

1 Reduction of renal parenchyma
  a Polycystic kidneys
  b Renal tumors
  c Hydatid cyst of the kidney
  d Traumatic lesions
  e Hypoplasia of the kidney
2 Perinephritis
3 Complete arterial obstruction
  a Thrombosis and atheromata of the renal artery
  b Emboli to the renal artery
4 Intermittent occlusion of the renal artery
  a Renal ptosis
5. External compression of the renal artery
  a Tumors of the pedicle
  b Aneurysms
6 Diminution of the calibre of the renal arteries
  a Congenital malformations
    (1) Hypoplasia of renal artery

b Arteriosclerosis
(1) Atheroma of the main renal artery
(2) Arteriolosclerosis
c. Inflammatory type of arterial lesions
(1) Lupus erythematosis disseminata
(2) Periarteritis nodosa
(3) Primary vascular nephritis
(4) Syphilis
(5) Thromboangiitis obliterans
7 Inflammatory lesions of the kidney
a Glomerulonephritis
8 Disorders of the urinary tract
a Obstructive disorders
(1) Lithiasis
(2) Hydronephrosis
(3) Pyonephrosis
(4) Congenital malformations
(5) Hypertrophy of the prostate
(6) Uterine prolapse
(7) Pelvic tumors
b Pyelonephritis
9 Venous obstruction
a External compression of the vein
b Congestive heart failure
10 Coarctation of the aorta

B HYPERTENSION PROBABLY OF RENAL ORIGIN
1. Essential hypertension
2 Malignant hypertension

C HYPERTENSION OF EXTRARENAL OR ILL-DEFINED ORIGIN
1 Endocrine
a Hypophysis
b Adrenal
c Ovary
d Toxemia of pregnancy
2. Nervous
a Trauma

b. Neoplasia
c Cerebral inflammatory processes
d Anxiety state

In this book we will concern ourselves only with hypertension of renal origin or of probable renal origin.

CHAPTER XIII

HYPERTENSION OF RENAL ORIGIN

Many gaps exist in our knowledge of the precise mechanism of production of human hypertension Although there is a large body of evidence suggesting that the kidney is intimately concerned in its production, this depends largely on its analogy to experimental renal hypertension in animals The fact that the course and behavior of all patients with chronic elevation of the diastolic pressure is similar, except for the rapidity with which the hypertensive disease progresses, is strong evidence suggesting a common, basic, underlying pathogenesis

Human hypertension frequently accompanies gross renal disease and yet is absent in perhaps half of all patients with clearly demonstrable disorders of the kidney. We have reviewed studies on the mechanism of production of renal hypertension (Chapter VIII) and have concluded that its production is best explained at the present time on the basis of ischemia of renal tissue despite certain important evidence to the contrary. The absence of ischemia despite gross abnormalities of renal structure and function may perhaps explain the lack of hypertension in these cases.

It has been shown experimentally that various procedures are capable of producing permanent or transitory hypertension. Pathologic lesions in human beings reproduce almost exactly each one of the procedures that have been devised to produce hypertension experimentally in animals. We do not believe that this is a coincidence since experimentation has always tended to reproduce conditions which have been considered as possible causes for a permanent elevation of blood pressure in the human disease For this reason, we have classified hypertension according to observations made in the experimental field. We do not mean to imply that the renal lesions in individual patients are necessarily responsible for the hypertension As will be pointed out, the renal lesions and the hypertension are frequently coincidental.

REDUCTION OF RENAL PARENCHYMA

Permanent hypertension by subtotal nephrectomy has been experimentally produced by some investigators. Others, on the other hand, have not been able to obtain positive results In human hypertension, kidney mass has at times been found diminished as in the case of polycystic kidneys, renal tumors, hydatid cysts of the kidney, traumatic lesions, and congenital hypoplasia of the kidney.

POLYCYSTIC KIDNEYS have been known for many years to be associated with hypertension. Braasch, in 1916, drew attention to this disorder which leads progressively and slowly to destruction of renal mass, and reproducing after a fashion experimental attempts to produce hypertension as discussed in Chapter I. As in the experimental field, hypertension appears frequently but not always The incidence of hypertension in polycystic disease varies according to different authors Fishberg (1939) found hypertension in 11 of 17 cases (65 per cent) Braasch and Schacht (1933) in a series of 190 cases found the systolic pressure to exceed 145 mm Hg in 61 per cent of the cases and the diastolic to exceed 90 mm. Hg in 55 per cent Schacht (1931) found hypertension in 75 per cent of 74 cases Zemitzsch (1939) noted hypertension in 143 of 180 cases with polycystic kidneys of which 139 had renal insufficiency and 4 had none, indicating that hypertension in these cases did not depend on renal excretory insufficiency In contrast to these statistics *which show a* high incidence of hypertension, Hollo and Kolbenheyer (1940) encountered hypertension in only 25 per cent of 36 cases

A high incidence of hypertension in patients with polycystic kidney disease is therefore undeniable Differences in published statistics

disease.

Without the help of experimental studies, it would be impossible to evaluate the mechanism of hypertension in these patients Hinman and Morison (1924) observed changes in the renal *circulation* of polycystic kidneys which they attributed largely to the mechanical factor of compression and displacement of the small intrarenal vessels produced by the cysts, the large vessels being spared Ritter and Baehr (1929) studied the vascular system of *these* kidneys exten-

sively by injecting opaque substances and found a more or less extensive vascular narrowing as a result of sclerosis According to the authors, this sclerosis was responsible for further atrophy of renal parenchyma, which led in turn to the further production of hypertension As in the case of experimental hypertension produced by amputation of renal tissue, the hypertension in patients with polycystic kidneys would appear to depend not on a lack of renal tissue but rather on the vascular changes appearing in the remainder of the kidney. These lesions consist of compression of renal vessels by the cystic process, envelopment of the vessels in the surrounding cicatricial tissue, and vascular sclerosis secondary to these processes

RENAL TUMORS also lead to destruction of renal tissue Two types of tumors are commonly found in the kidney—hypernephroma and Wilms' sarcoma The frequency of hypertension in association with these tumors has been found to be variable by different authors (Abeshouse, 1941) Morlock and Horton (1936), in a study made on 491 cases (335 hypernephromas and the rest with other types of tumors), found hypertension with equal frequency in both groups and did not observe in any of them a significant fall of blood pressure after nephrectomy. The relation between hypertension and these tumors has, however, been demonstrated in some cases In a number of instances, removal of the tumor has been followed by a fall of blood pressure In 9 of 21 cases of hypernephroma with hypertension followed by Braasch, Walters and Hammer (1910a, b), a permanent fall of blood pressure followed operation Horton (1910) described an interesting case of a patient with hypernephroma and hypertension cured by nephrectomy Years later the hypertension returned together with the appearance of a metastasis of the original umor

Renal sarcomas or Wilms' tumors may also be accompanied by ypertension. Koons and Ruch (1940) described a case of a seven-ar-old girl with hypertension cured by nephrectomy, despite the istence of tumor metastases in other parts of the body Bradley l Pincoffs (1938) observed hypertension in five patients with ms' tumors In two of them the pressure fell after its removal, but rary to the observations of Koons and Ruch, the pressure became ited again with the reappearance of the tumor Daniel (1939)

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Less clear is the mechanism by which the hypertension is produced in these individuals. The possible production by the tumor of pressor substances responsible for the hypertension appears to be supported by the fact that in some cases, as in that of Horton (1940), the hypertension returned when metastases of the original tumor *appeared On the other hand, the occurrence of cases in which the* blood pressure has fallen permanently despite the existence of tumor metastases and the fact that Daniel was not able to find pressor substances in the tumor cells make this possibility unlikely.

It seems probable that the tumors produce changes in the renal vascular system and that these in turn are concerned in the production of the hypertension. As Abeshouse (1941) noted, the tumor may *alter the renal circulation* (a) by *compression* of the kidney vessels adjacent to the tumor, (b) by compression of the vascular pedicle, (c) by compression or torsion of the vessels by renal *displacement*, (d) by infiltration of the renal parenchyma by the tumor, or (e) by thrombosis of the large vessels of one or both kidneys as a *result of* tumor infiltration

Renal vascular changes have not been studied extensively in patients with renal tumors. It is possible that their presence or absence determines the presence or absence of hypertension in a given case. *The reappearance of hypertension* some time after the operation may possibly be conditioned by the development of vascular lesions in the opposite kidney as a *result of long-continued* preoperative hypertension. It is also possible that the recurrence of the hypertension is due, as Daniel believed, to the invasion *of the renal pedicle* of the opposite kidney by the tumor.

HYDATID CYSTS involve the kidney in 2 2 per cent of cases of echinococcosis[1] The frequency with which hypertension appears in such patients has not been studied. Davson (1941) cites the case of a 25-year-old woman who died of malignant hypertension. At autopsy,

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TRAUMATIC LESIONS Cases of hypertension observed following trauma are related to destruction of the renal parenchyma Only a few cases of hypertension in association with traumatic renal processes have been described in the literature Nesbit and Ratliff (1940) referred to a case of hypertension developing from a cystic ischemic nephropathy of traumatic origin Braasch, Walters and Hammer (1940a, b) observed two cases of nephrosclerosis with hypertension appearing soon after trauma Farrell and Young (1942) described a case of hypertension secondary to a post-traumatic hemorrhagic cyst of the kidney, cured by nephrectomy

In addition to accidental trauma, surgical injuries may at times cause hypertension In this regard, the observations of Braasch, Walters and Hammer (1940a, b) are pertinent They observed hypertension to develop immediately following conservative renal operations in 14 patients In each case the blood pressure returned to normal after nephrectomy Abeshouse (1941) also described a patient with renal stones who developed hypertension seven months after their removal Trauma frequently produces chronic renal changes such as fibrosis, hydronephrosis, perinephric calcification, and so forth Permanent hypertension may be associated with these conditions. Despite this and the cases of hypertension of traumatic origin which have been described, the importance of trauma as an etiologic factor of hypertension has not been studied extensively Although traumatic processes can occasion intrarenal circulatory changes capable of producing permanent hypertension as Schroeder (1942) was able to demonstrate experimentally in rats, a systematic study is needed to elucidate the precise relationship between trauma and human hypertension.

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mentally in the hands of Hartman, Bolliger and Doub (1929) and Page (1936b). Dean and Abels (1944) described the case of a 20-year-old woman who received approximately 4,500 roentgens over the left kidney for a left upper quadrant tumor. Blood pressure and urograms were normal at the time. Seven years later, the blood pressure was 184/125 mm. Hg, urograms showed a shrunken left kidney, and glomerular filtration, tubular mass, and renal blood flow were markedly diminished on the left. Following removal of the left kidney, the blood pressure returned to normal and remained normal for at least 14 months The kidney showed extensive fibrosis and obliterative endarteritis which the authors attributed to the previous irradiation.

CONGENITAL HYPOPLASIA OF THE KIDNEY Hypertension has been related to congenital hypoplasia of the kidney. Ask-Upmark (1929) believed that this anomaly was the most frequent cause of malignant nephrosclerosis in young individuals Cases of this type have been described by Leiter (1938), Oppenheimer, Klemperer and Moschkowitz (1939), Clark (1940), DeTakats and Scupham (1940), Killian and Calvin (1941) and O'Conor (1942). Patients with congenital hypoplastic kidneys do not, however, invariably have an elevation of blood pressure. It is more common, indeed, for the blood pressure to be normal. In three cases studied by Abeshouse (1941), the blood pressure was normal. Hypertension was not found in any of the five cases studied by Braasch, Walters and Hammer (1940). As in the majority of cases with renal disease, excretory renal insufficiency, although frequently present, bears no relation to the presence of hypertension From pathologic studies, it is apparent that the most important factor in the production of hypertension is the state of the renal vessels Ask-Upmark found a marked sclerosis of the arteries and arterioles of the renal parenchyma in all his cases. Similar changes were found in the majority of the cases cited above

It is of interest, however, that the existence of a vascular sclerosis [illegible] congenital hypoplastic kidneys, wrote: "Is the hypertension [illegible] related to obstruction of blood flow by the contraction of fibrotic kidneys? On this assumption it is difficult to explain the absence of hypertension in at least 75 per cent of the children with renal dwarf-

ism and renal rickets, associated with congenital dilatation of the urinary tract and severe fibrotic atrophy of the kidneys"

We believe that the cause of the hypertension is not the presence of sclerosis or of primary vascular hypoplasia but rather the result of renal ischemia. Although in hypoplastic kidneys there is usually a sclerosis or a vascular hypoplasia which markedly reduces the blood flow in relation to the normal kidney, this reduction may well parallel the reduced mass of functioning renal tissue, in which case there would be no renal ischemia In other cases, the co-existence of congenital changes in the urinary tract possibly leads to the simultaneous formation of large hydronephrotic sacs which, for reasons to be discussed later, may prevent the appearance of hypertension despite the existence of a certain degree of ischemia Pyelonephritis, which is a common complication of congenital disorders of the kidney, may perhaps be a factor in the production of hypertension in a certain number of these patients As we shall see, pyelonephritis frequently produces an obliterative endarteritis which may well lead to renal ischemia and hypertension.

Only an extensive physiologic and pathologic study of hypoplastic kidneys would reveal the rôle of each one of these factors and explain why hypertension is present or absent in individual cases

PERINEPHRITIS

The appearance of permanent or transitory hypertension as a result of perirenal lesions has been observed in a few patients Sobel (1941) described the case of an eight-year-old boy who immediately after injury developed a perirenal hematoma Hypertension appeared coincidentally and persisted for several weeks, finally disappearing as the hematoma reabsorbed. A similar case is that of Engel (1940) where hypertension lasted 11 days in association with typical signs of an intracapsular renal hematoma Both cases are examples of transitory hypertension, similar in every respect to the experimental observations of Alwens (1909) who constricted the kidney in an oncometer. Farrel and Young (1942) described the case of an 18-year-old student in whom hypertension was incidentally found. The only suggestive factor in the history was trauma in the renal region at the age of six The diagnosis of a perirenal tumor was made. Operation showed a large cystic hematoma containing approximately 800 cc. of blood which was well organized and which enveloped and flat-

tened the corresponding kidney. The kidney was thickened, the margins were cartilaginoid, and the walls of the arteries were thickened and sclerosed. Removal of the kidney was followed by a return of the blood pressure to normal A similar case was that of Nesbit and Ratliff (1940) occurring in a 32-year-old patient who had suffered trauma in the lumbar region ten years previously. Both of these cases are similar to the experimental hypertension produced by Page (1939b) by wrapping cellophane around the kidneys of animals Koons and Ruch (1940), in discussing their case of hypertension produced by a Wilms' tumor which completely enveloped the kidney, likewise suggested that the elevation of blood pressure might have been due to compression of the kidney by the tumor.

Braasch and Wood (1942a, b), in a study of 70 cases of perinephritis, found a relationship between this lesion and hypertension in only 4.28 per cent This incidence was less than that found statistically in unselected subjects. The case reports described above, however, suggest the possibility that perinephritis from various inflammatory disorders or from trauma is important in the production of hypertension in certain individual cases It would be interesting to make a systematic study of the blood pressure in cases of this type since the appearance of hypertension may be asymptomatic for long periods of time. If the hypertension is not recognized for years, irreparable lesions may appear in the circulatory system and in the vessels of the opposite kidney.

COMPLETE ARTERIAL OBSTRUCTION

We have seen that some degree of hypertension may be produced experimentally by complete occlusion of the renal arteries In man, it has been shown repeatedly that hypertension is associated with similar alterations of the renal circulation produced by thrombosis, emboli, or atheromas in one or both renal arteries.

THROMBOSIS AND ATHEROMATOSIS. In 1939, Welty analyzed 11 cases of obstruction of the renal circulation by thrombosis, *in all of which there was hypertension.* Ronald and Leslie (1940) described the case of a 43-year-old hypertensive patient in whom autopsy revealed thrombosis of the abdominal aorta with complete thrombosis of the left renal artery and partial thrombosis of the right Saphir and Ballinger (1940) observed a patient with complete

unilateral occlusion of the renal artery accompanied by chronic hypertension. Soon after an accident, this patient developed hypertension and years later, autopsy revealed an organized thrombus which obstructed the left renal artery

Although more rare, cases are described in the literature in which complete obstruction of the renal arteries is due to atheromatous plaques Stewart (1940) described the case of a hypertensive patient with an atheromatous obstruction of the mouth of both renal arteries which had led to atrophy of both kidneys with the exception of one small area in each which was nourished by an aberrant collateral artery.

As in experimental complete renal ischemia, the hypertension observed in these patients is best explained by the passage of pressor substances into the general circulation through the abundant collateral circulation This circulation may in some cases lead to a prolonged survival despite the existence of complete arterial obstruction, especially when the latter is the result of a chronic process

EMBOLI. The appearance of hypertension as a result of embolic accidents to the renal arteries had not been mentioned until recently except in isolated cases Prinzmetal, Hiatt and Tragerman [illegible] referred to a case of embolic occulsion of both renal arteries with resultant hypertension The vascular system of these kidneys was perfused and the perfusion fluid contained a substance with pressor activity when injected into a dog. This substance was similar to that found in the perfusion fluid of kidneys following experimental complete renal ischemia This case is entirely analogous to that observed by several authors after experimental occlusion of the renal arteries

Fishberg (1942) recently described four cases in which hypertension appeared as a result of emboli to the kidney, one of them following myocardial infarction, two in patients with [illegible] fibrillation and mitral stenosis, and a fourth in a patient with mitral stenosis and fracture of the femur Hypertension secondary to embolic infarcts of the kidney was studied statistically by Hoxie and Coggin (1940), who observed that 33 per cent of [illegible] patients with renal infarcts had hypertension

Hypertension from renal emboli may disappear [illegible] the infarcts or may persist and become chronic [illegible] [illegible]

ination of the kidney in these cases may reveal vascular processes in the zones adjacent to the infarct simulating glomerulitis or necrotizing arteriolitis (*Klemperer and Otani, 1931*).

The production of acute hypertension in cases of renal embolic infarction is explainable on the basis of a liberation of pressor substances as a result of acute renal ischemia. Chronic hypertension in some cases may well be the result of renal ischemia produced by vascular lesions in the zone adjacent to the infarct

The presence or absence of hypertension in cases with renal emboli should theoretically depend on the size of the infarcted area and on the existence of a sufficient circulation to allow pressor substances to escape into the general circulation In addition, other factors of a more general nature may favor or inhibit the appearance of hypertension Thus, patients with embolic phenomena may go into shock with a resulting fall of blood pressure which would mask the hypertension An associated fever would tend to produce a fall of blood pressure In other cases there may be, as Fishberg suggests, an individual predisposition to hypertension, the nature of which is difficult to appraise

INTERMITTENT OCCLUSION OF THE RENAL ARTERY

Experimental intermittent occlusion of the renal pedicle in man has been carried out in the course of operative procedures on this organ by Quinby, Dexter, Sandmeyer, and Haynes (1945) These authors demonstrated small amounts of renin in the renal venous blood of dogs and man on re-establishing the renal circulation after 10 to 12 minutes of complete ischemia No elevation of blood pressure was obtained in either species as a result of *this short period* of complete ischemia.

Intermittent occlusion of the renal artery experimentally has its clinical counterpart in the [illegible] from nephroptosis recently described by [illegible] These investigators *observed that*, [illegible] blood pressure fell rapidly if they were placed in the recumbent position By means of inulin and diodrast clearances, they showed that these patients had a considerable reduction of renal blood flow in the erect position (figure 90), from which they concluded that their hypertension was produced by partial ischemia in the upright posi-

tion. The rapid formation of pressor substances during experimental constriction of the renal artery observed by Quinby, Dexter, Sandmeyer and Haynes supports this interpretation Recently Riskind and

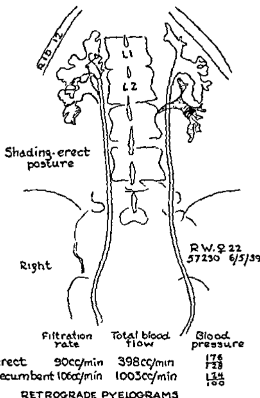


FIGURE 90 VARIATION OF RENAL BLOOD FLOW IN A PATIENT WITH ORTHOSTATIC HYPERTENSION

Superimposed tracings of retrograde pyelograms in upright and recumbent positions Note how renal blood flow and glomerular filtration are reduced and the blood pressure increased in the erect position (After McCann and Romansky, Tr A. Am Physicians, 1940, 55, 240)

Greene (1912) described a case of ptosis and rotation of the right kidney with an associated hypertension which was improved by the use of an orthopedic belt. Removal of the belt on one occasion was followed by an elevation of blood pressure.

EXTERNAL COMPRESSION OF THE RENAL ARTERY

After Goldblatt and his collaborators had shown that permanent *hypertension could be produced by reducing renal blood flow*, clinical and pathologic studies were made with the object of demonstrating the existence of a similar mechanism in human hypertension. It has been shown that human hypertension is apparently caused in some instances by chronic renal ischemia produced by changes in the renal artery or in its main branches. Diminution of blood flow to the kidney by external compression of the pedicle, reproducing *exactly the experiments of Goldblatt, has been demonstrated in* a clearcut manner in a few cases Blatt and Page (1939) described a case of lymphosarcoma with compression of the renal vessels Baeroe (1942) reported hypertension from constriction of the renal artery due to a dissecting aneurysm of the aorta Hoffman (1942) described the case of a 23-year-old hypertensive who at autopsy showed a saccular aneurysm of the aorta which pressed against the renal pedicle. *Compression of the renal pedicle may be a cause* of ischemia in certain cases with hydronephrosis or adjacent inflammatory processes. We have already mentioned that Koons and Ruch (1940) believed that renal tumors could spread to the pedicle of the opposite kidney, compress the corresponding artery, and thus cause persistent hypertension.

It is perfectly possible that hypertension may be produced in man under certain circumstances by permanent compression of the renal artery from disease processes. In the cases cited, this mechanism appears to be definite That tumors and other disorders around the renal pedicle are responsible for renal ischemia is probable *but has* not been definitely proven

DIMINUTION OF THE CALIBRE OF THE RENAL ARTERY

CONGENITAL MALFORMATIONS Congenital hypoplasia of the renal arteries has been considered by some authors as a possible cause of ischemia and hypertension (Weiss, 1940) This malforma*tion, however, is frequently* associated with congenital hypoplasia of the kidney, the relation of which with hypertension has already been discussed

The calibre of the renal artery may be reduced by other congenital defects Leadbetter and Burkland (1938) reported the case of a boy

with hypertension in whom the kidney was located in the pelvis. Following nephrectomy, the hypertension disappeared On pathologic examination, the renal artery was found to be almost completely obstructed by a smooth muscle plug which narrowed the lumen of the vessel

ARTERIOSCLEROSIS OF THE RENAL ARTERY AND OF ITS MAIN BRANCHES Goldblatt (1938b) was the first to show that hypertension was associated in some cases with sclerosis and narrowing of the orifice or of the lumen of the main renal artery Leiter (1938) somewhat later described a case of chronic hypertension associated with complete arteriosclerotic occlusion of the left renal artery and incomplete occlusion of the right Freeman and Hartley (1938) almost simultaneously reported hypertension in a patient who was nephrectomized because of an accident At autopsy an atheromatous plaque was found to obstruct the mouth of the renal artery Similar cases were described later by Blackman (1939), Stewart (1940), Saphir and Ballinger (1940) and Laas (1940) The importance of unilateral narrowing has been emphasized by Oppenheimer, Klemperer and Moschkowitz (1939) who showed that in 18 cases who anatomically showed unilateral narrowing of the renal artery, 15 had hypertension Blackman (1939) found a narrowing of the renal artery at or near its mouth in 86 per cent of cases with hypertension Richardson (1943) recently reported stenosis of one or both renal arteries by arteriosclerotic plaques in 25 of 32 hypertensive patients studied at autopsy

Kahn and Laipply (1942) observed a high incidence of bilateral arteriosclerosis in 1,000 hypertensive patients studied pathologically Friedman, Moschkowitz and Marrus (1942) observed arteriosclerosis of the renal vessels in 23 of 28 hypertensive patients who were nephrectomized

Lisa, Eckstein and Solomon (1943) reported that in 100 consecutive cases coming to autopsy in which blood pressure readings were available, hypertension was present in 56 while 44 were nonhypertensive. No appreciable difference in the average diameter of the renal artery was found in the two groups Yuile (1944) recently reviewed the literature on the relation of obstructive lesions of the main renal artery and hypertension and concluded that such a relationship does

exist in certain cases. This author pointed out the desirability of a closer anatomical and physiologic correlation.

From these studies it may be concluded that isolated lesions of one or both renal arteries are frequently observed in patients with hypertension. Their importance as an etiologic factor, however, remains doubtful in many cases. A relationship between these lesions and hypertension can be justifiably assumed if the obstruction is considerable and if there are no vascular lesions in the vessels within the same kidney, such as occurs in animals following constriction of the renal artery If the hypertension is due to the lesion in the renal artery, one would expect that benefit would follow improvement of the collateral circulation to the kidney by means of such procedures as omentopexy as it does in animals with experimental hypertension from constriction of the renal artery, or nephrectomy providing irreversible vascular lesions had not appeared in the opposite kidney.

It should be borne in mind that unilateral lesions of the kidney are capable of producing hypertension since the success of therapeutic nephrectomy can be predicted, at least to some extent, by determining effective blood flow to each kidney separately, by careful evaluation of the duration of the hypertension, by taking into account the age of the patient, and by examining the retina for vascular lesions

Bilateral arteriosclerosis of the renal vessels and sclerosis of the small arterioles are, as we shall see later, common findings in essential hypertension. Their importance as an etiologic factor will be discussed in Chapter XIV.

INFLAMMATORY DISORDERS OF THE ARTERIES. Two rare diseases of this type may involve the renal arteries: Periarteritis nodosa and lupus erythematosus disseminata. Gruber (1926) directed attention to involvement of the renal vessels in periarteritis nodosa. Of 108 patients with this disease, the renal vessels were found to be affected in 74. Isolated cases of hypertension in association with this arteritis have been described by Hess (1924), Singer (1927), Bau (1934), Bernstein (1935), Fishberg (1939) and Grant (1940) and many others Banks (1941) has discussed this and related disorders Spiegel (1936) found hypertension in 9 of 15 cases with periarteritis nodosa The recent experimental production of this disorder by the

administration of sulfonamides and foreign proteins (Rich, 1942, Rich and Gregory, 1943) should lead to a better understanding of the relationship of periarteritis nodosa to renal involvement and hypertension.

Lupus erythematosus disseminata was first described by Kaposi (1872). Libman and Sacks (1924) described this disorder under the name of atypical verrucous endocarditis and called attention to the "wire loop" changes in the glomeruli which are frequently associated with hypertension

A syndrome has been described by Keegan under the name of primary vascular nephritis in which involvement of the renal vessels appears to be primary. When this becomes chronic, it is accompanied by hypertension Grant (1910) believed that this disorder should be especially considered in cases of malignant hypertension Arteritis from other causes such as syphilis or thromboangiitis obliterans (Leiter, 1938) may be located in the renal vessels and be associated with hypertension. Although not of an inflammatory nature, it might be well to mention here the syndrome of diabetes, hypertension, edema and albuminuria described by Kimmelstiel and Wilson (1936), Newburger and Peters (1939), and many others under the name of intercapillary glomerulosclerosis This syndrome, characterized anatomically by considerable fatty degeneration and arteriolar sclerosis including the afferent arteriole of the glomerulus with extension into the glomeruli, is typically characterized by hypertension From the renal histology, renal ischemia may be suspected as the cause of the hypertension

INFLAMMATORY LESIONS OF THE KIDNEY

GLOMERULONEPHRITIS Attempts have been made to reproduce human glomerulonephritis by producing renal lesions with nephrotoxic sera and by administering various substances to animals Hypertension, edema and hematuria are the triad of manifestations on which the diagnosis of this disease is based. The frequency of hypertension is not the same in all forms of glomerulonephritis. In the acute form, hypertension may or may not be present It has a tendency to be mild or absent in children although in some cases it may be severe Fishberg (1939) observed that patients with acute glomerulonephritis quite frequently have no elevation of blood pres-

sure despite subsequent pathologic evidence of typical and advanced lesions of the renal vessels. In the subacute and chronic forms, however, hypertension is usually present.

The hypertension appearing in the course of acute glomerulonephritis is generally believed to be of renal origin and renin has actually been detected in the systemic blood of two patients in which it was investigated by us (unpublished) and of one patient by Dexter and Haynes (1944). A systematic study of this point should be made. *Perhaps the variable appearance of hypertension in the different* stages of glomerulonephritis is due to the character of the pathologic lesions and of renal functional changes at each stage of the disease.

Acute glomerulonephritis is characterized pathologically by endocapillaritis of the glomerular loops. The process is diffusely spread throughout the kidneys. In severe cases, swelling and proliferation of the glomerular endothelium and accumulation of inflammatory exudate and leukocytes within the loops produce blockage of the glomerular capillaries and diffuse capillary ischemia as Lohlein (1917) described and as others have subsequently confirmed Since it is an acute inflammatory type of lesion, there may perhaps be an actual hyperemia of renal tissue as Dr. Stanley Bradley (personal communication, 1945) has found using clearance methods, and not an ischemia as the renal histology suggests.

As glomerulonephritis becomes chronic, it is characterized pathologically by progressive thickening of the intima, and by hypertrophy of the media and muscularis of arterioles, disappearance of functioning elements and replacement fibrosis The picture is one of progressive ischemia which perhaps explains the gradual rise of blood pressure Opposed to this, however, are the physiologic observations of Earle, Taggart and Shannon (1944) who studied the renal physiology of patients with diffuse glomerulonephritis as early as three weeks and as late as nine years after the onset of acute glomerulonephritis Using clearance methods, glomerular filtration rate, renal blood flow, and tubular excretory mass became progressively diminished as the disease advanced. Transient hyperemia, even in the presence of hypertension was sometimes noted The presence of hypertension could not be specifically related to the residual kidney mass although it was not infrequent when there was more than a 40 per cent reduction in tubular excretory mass.

The vascular lesions of glomerulonephritis, known since the time

TABLE IV. INCIDENCE OF HYPERTENSION IN SURGICAL DISORDERS OF THE KIDNEY

Diagnosis	Number of Patients	Systolic Pressure 145 mm. Hg or more		Systolic Pressure 160 mm Hg or more	
		Number of Cases	%	Number of Cases	%
Adenocarcinoma	138	38	27.7	19	13.9
Tuberculosis	158	12	7.6	4	2 5
Atrophic pyelonephritis	43	20	46 5	15	34 9
Nonatrophic pyelonephritis	70	13	18.6	6	8 6
Hydronephrosis	372	51	13 7	21	5 6
Hydronephrosis and lithiasis	577	125	20 9	82	14.2
Lithiasis with infection	164	37	22 5	19	11.6
Lithiasis without infection	52	3	5.7	0	0 0
Miscellaneous	111	20	18.0	9	8 1
Total	1684	315	18.7	175	10 4

In a pyelographic study performed on 212 hypertensive patients, Palmer, Chute, Crone and Castleman (1940) found unilateral acquired or congenital deformities of the renal pelvis in 34 to 16 per cent Pearman, Thompson and Allen (1940), in 500 selected cases out of a total of 12,000 hypertensives, found 205 with pyelographic abnormalities. In patients with surgical disorders of the kidney, however, they did not find any greater incidence of hypertension than in a similar group of patients with other surgical disorders (gall bladder disease, nontoxic thyroid adenomas, and so forth). In the total number of hypertensive patients, they did not find a greater frequency of surgical disorders of the kidney than of other organs such as the gall bladder and stomach. These results are in agreement with the findings of Crabtree and Chaset (1940) in 150 nephrectomized patients. Schroeder and Steele (1941) found that 113 of 178 cases diagnosed as essential hypertension had renal abnormalities by pyelography. Ratliff and Conger (1942), in a pyelographic study performed on 340 hypertensives with urinary symptoms, found that only 17 had a definite disorder of the urinary tract Recently Shrader, Young and Page (1943), in a pyelographic study of unselected hypertensive patients, concluded that the frequency of urographic abnormalities was no greater in these patients than in patients with normal blood pressure.

Wosika, Jung and Maher (1942) in a statistical study on 2,002 autopsies found that there was a higher incidence of urologic lesions in hypertensive patients than in normal patients

Ravich (1941) believed that the type of renal pelvis played some

rôle in the production of renal ischemia. He emphasized the importance of the intrarenal pelvis Later studies by Sarnoff (1942), Hyman and Schlossman (1942), and Stofer and Kline (1943) have shown that this factor is of no importance.

These various studies appear to indicate that surgical disorders of the urinary excretory tract are of little importance as etiologic factors of hypertension There is no doubt, however, that there is a relationship in certain individual cases reported in the literature · Other disorders may interfere with ureteral emptying We refer to prolapse of the uterus and pelvic tumors in the female, and to hypertrophy of the prostate in the male

Hypertension from urinary obstruction of genital origin was observed first by Passler (1906) who described a case of hypertension and anuria of 12 days' duration caused by the extension of a carcinoma of the neck of the uterus Brasch in 1911 described similar cases Halban and Tandler in 1907 drew attention to the frequency of stasis and ureteral dilatation as a result of uterine prolapse, and Wosika and Maher (1939) recently emphasized the frequency with which uterine prolapse is associated with hypertension In 97 cases studied, 76 per cent had hypertension These results have recently been confirmed by Everett and Scott (1942) who observed a greater incidence of hypertension in patients with large pelvic tumors and prolapse of the uterus than in normal women of the same age

In man, the relation between retention of urine by prostatic hypertrophy and hypertension has been observed with relative frequency Von Monakow and Mayer (1918) demonstrated that this hypertension disappeared on relieving the urinary obstruction. O'Conor (1920) studied 56 patients with prostatic hypertrophy, 55 of whom were operated on and followed after operation. It was observed that drainage of the bladder in hypertensive patients with urinary obstruction produced a marked fall of blood pressure in the course of the first 48 hours, and that by maintaining drainage, the pressure could be kept at a more or less steady level, below that initially found, after operation and even during convalescence. In the 55 operated cases, only one experienced a slight rise of pressure above that observed at the beginning of treatment In 10 per cent, the pressure eventually returned to the initial level while in the remainder it remained permanently below the level observed before the urinary retention.

We may conclude, therefore, that although in some patients with a unilateral lesion of the excretory tract hypertension may appear, in the majority of cases it is independent of the renal lesion. On the other hand, hypertension is frequent in cases with bilateral urinary retention This has long been appreciated and supports the old theory of Braun who tried to explain hypertension by obstruction of blood flow through the kidney produced by an increase of pressure in the urinary tract which was transmitted to the tubules and glomeruli with a resulting compression of the capillary loops While this purely mechanical factor in the production of hypertension of renal origin has not been borne out by animal experimentation, experimental analogy suggests that the hypertension may be due to a liberation of pressor substances of ischemic origin.

By means of animal experiments, Goldblatt, Kahn and Lewis (1941) have thrown light on the mechanism of hypertension in patients with disorders of the urinary tract. These investigators showed that occlusion of one ureter did not produce hypertension while occlusion of both ureters usually did. They postulated that ureteral occlusion might diminish the amount of pressor substances passing into the general circulation in those cases in which the kidney had been made ischemic by constriction of the renal artery. According to this concept, there would be a balance between the degree of ischemia produced by ureteral obstruction and the prevention of the passage of pressor substances into the blood created by the same urinary obstruction In unilateral lesions, even in the case of renal ischemia, hypertension is slight or may not appear possibly because of an insufficient quantity of pressor substances passing into the systemic circulation In cases with bilateral lesions, the quantity of pressor substances is presumably greater since both kidneys are involved in its formation. This may perhaps account for the greater incidence of hypertension. We believe that another factor may be involved in cases with unilateral lesions. The presence of a normal kidney, which as we have seen possesses a "protective action," may well contribute to explaining the differences observed in the behavior of the blood pressure in association with unilateral and bilateral obstructive lesions.

PYELONEPHRITIS. As an etiologic agent for hypertension, pyelonephritis is the only process of real importance in this group.

Longcope and Winkenwerder in 1933 called attention to the frequency with which bilateral contracted kidneys from pyelonephritis are observed Later Longcope (1937) emphasized the frequent association of this disease with hypertension Weiss and Parker, in a series of important publications (1938, 1939), believed that pyelonephritis, especially in the chronic and cicatricial stage, was frequently associated with hypertension, not only when bilateral but also when unilateral. This has been confirmed by numerous investigators[2] in such a manner as to leave no doubt In children pyelonephritis is frequently associated with hypertension Kimmel (1942) found hypertension in ten per cent of children afflicted with pyelonephritis

The incidence of hypertension depends on whether the lesion is unilateral or bilateral (Shure, 1942) If the process is bilateral, hypertension usually exists In unilateral pyelonephritis, the incidence of hypertension varies particularly with the duration of the renal process If the disorder is of recent origin, the blood pressure is usually unchanged When the pyelonephritis becomes chronic, the incidence of hypertension increases Crabtree (1940) found hypertension in 11 of 75 patients with pyelonephritis of 5 to 18 years' duration Braasch and Jacobson (1940a, b), in a study made on 180 patients with pyelonephritis, found hypertension in 22 per cent of the cases of 1 to 5 years' duration, in 26 per cent in 5 to 10 years, and in 29 per cent of those over 10 years This difference is even more striking when applied to patients under 50 years of age When the disease reaches the stage of atrophic kidneys, the hypertension is more frequent Braasch, Walters and Hammer (1940a, b) found hypertension in 20 of 43 patients at this stage Hypertension is independent of the functional state of the kidney and of the degree of infection in the kidney. It frequently appears when the disease enters the healing phase The condition of the renal vessels in pyelonephritis, according to Weiss and Parker (1939, 1940), is of prime importance with regard to the appearance of hypertension These investigators observed pyelonephritis to be frequently accompanied by vascular changes, arteritis, or

[2] Butler (1937), Barker and Walters (1938, 1940a, b, c), Barney and Suby (1939), Crabtree and Prien (1939), McIntyre (1939) Siler (1940), Patch, Rhea and Codnere (1940), Engel (1940), Nesbit and Ratliff (1941), Lobo-Onell and Díaz Muñoz (1941), Killian and Calvin (1941), Baggenstoss and Barker (1941a b), O Connor (1942), Taylor (1942), Powers and Murray (1942), Bowen and Kutzman (1942)

necrotizing arteriolitis, which bore a close relation to the degree and severity of the hypertension observed in these patients. It seems likely that vascular changes in the kidney lead to renal ischemia with the resulting liberation of pressor substances and appearance of hypertension. The degree and severity of the hypertension would be conditioned by the character of the vascular lesions.

The inconstancy of hypertension in cases with pyelonephritic contracted kidneys may perhaps be due to a number of factors such as (1) the degree of ischemia which depends upon the extent of the vascular lesions, (2) the amount of ischemic renal parenchyma which is dependent upon the extent of the destruction of kidney tissue, and (3) the degree of urinary stasis. An increase of ischemia and of the amount of ischemic tissue would tend to produce pressor substances and to favor the appearance of hypertension. An increase of urinary stasis, on the other hand, might create an obstacle to the passage of these substances into the systemic circulation thereby hindering the appearance of hypertension

VENOUS OBSTRUCTION

Hypertension from pure venous obstruction has not been observed Hoffman (1942) recently described a patient with hypertension associated with compression of the renal pedicle by a saccular aneurysm of the descending aorta Anatomic study of the kidney showed marked stasis due to venous compression It is difficult to judge how much this had to do with the rise of blood pressure.

Hypertension appearing in the course of heart disease is possibly related to this mechanism Levine and Fulton (1928) observed hypertension in more than 50 per cent of their patients with rheumatic mitral stenosis. This has recently been refuted by Horns (1941) In tricuspid disease with chronic circulatory congestion, however, we have frequently observed hypertension. Although the hypertension may be due to other causes, it is possible that changes in the renal circulation play some rôle Blood pressure tends to be elevated in other types of cardiac failure in which marked venous stasis exists, such as in right heart failure secondary to pulmonary disease. It would be interesting to study the relationship of renal ischemia from venous stasis to the presence of hypertension in these patients.

COARCTATION OF THE AORTA

Hypertension in young individuals is occasionally due to stenosis of the aortic isthmus Lewis (1933) emphasized the frequency with which coarctation of the aorta is accompanied by hypertension. This hypertension is peculiar in that in the majority of cases it is found only in the upper limbs when recorded by auscultatory methods It might logically be thought that with obstruction of this vessel the hypertension in the upper extremities would be due to the shunting of larger amounts of blood to the upper extremities Blumgart, Lawrence and Ernstene (1931) found a normal blood pressure in two patients with this disorder. They, therefore, suggested that the hypertension observed in the large vessels was due to circulatory obstruction produced by diminution in the calibre of the aorta Prinzmetal and Wilson (1936) observed that the application of heat to one of the upper limbs produced an increase of blood flow in the opposite arm which was greater than that observed in normal subjects, from which they concluded that there was a vasoconstriction or vascular hyper-reaction of vasomotor origin in these patients. Pickering (1936b), although obtaining results similar to those of Prinzmetal and Wilson, attributed the blood pressure changes observed in these patients to local changes or possibly hypoplasia of the vessels. He did not believe that a mechanism could exist which could produce reflex hypertonia only in the upper limbs. Stewart, Haskell, and Evans (1941) reported a slight increase of peripheral blood flow, skin temperature, and rectal temperature in patients with coarctation of the aorta as compared with normal control subjects

The above investigations made no reference to a possible relation between the hypertension and the kidney. Certain studies, however, have brought out the importance of this relationship Steele and Cohn (1938) found an increase of diastolic pressure in the femoral artery in patients with coarctation of the aorta Steele (1941), in an analysis of 217 cases reported in the literature, found a systolic hypertension in all of the cases and a diastolic hypertension in half of the cases The diastolic pressure of the legs was shown to be elevated in 65 of the cases reviewed In some of them it was shown to be higher than that observed in the arms despite a definite diminution in pulse pressure in 12 of them The generalized elevation of diastolic

pressure *indicates that* in association with stenosis of the aortic isthmus, there is a *generalized* increase of peripheral resistance. This would suggest a *humoral origin* for this type of hypertension.

This conclusion is further *supported* by the experimental studies of Goldblatt and Kahn (1938), Rytand (1938b), Steele (1939), and Ogden, Page and Hildebrand (1942) as mentioned in Chapter I. which conclusively demonstrate that hypertension from experimental aortic constriction appears only when the aorta is constricted above the point of origin of the renal vessels.

Friedman, Selzer, Rosenblum, McLean and Picard (1941) found that despite the existence of a normal glomerular filtration, in 6 cases with coarctation of the aorta, there was a uniform and definite reduction of renal blood flow, indicating the presence of renal ischemia. The demonstration of a generalized increase of peripheral resistance and of renal ischemia in man bears a close parallelism to experimental observations and strongly suggests a renal origin of the hypertension associated with human coarctation of the aorta.

Although hypertension is frequently absent in patients with renal disease, pathologic processes reproduce the various methods which have been employed for the production of hypertension in experimental animals

Reduction of renal parenchyma is represented by polycystic kidneys, renal tumors, hydatid cysts, traumatic lesions, and congenital hypoplasia of the kidney Experimental perinephritis has its counter part in perinephritis of human beings. Complete arterial obstruction may be the result of thrombosis, atheroma, or emboli in the renal arteries Intermittent occlusion of the pedicle is seen in the syndrome of orthostatic hypertension resulting from renal ptosis Compression of the renal arteries occurs as a result of tumors or of other lesions which can constrict the renal pedicle. Reduction in the calibre of the renal arteries is found in congenital, arteriosclerotic or inflammatory lesions of the vessels. Inflammatory lesions of the parenchyma occur in glomerulonephritis Ureteral obstruction results from disorders of the urinary tract. Venous obstruction occurs as a result of venous compression or of chronic passive congestion from cardiac insufficiency And finally, experimental coarctation of the aorta reproduces a similar picture of congenital origin seen in human beings.

As in the experimental animal, all these diseases may be accompanied by hypertension when there are associated vascular lesions. The relation between hypertension and the renal lesions can not always be proven since detailed physiologic and pathologic studies are necessary to establish such a relationship The relationship may be suspected from analogy with experimental hypertension and especially when hypertension appears in a young individual Studies of renal blood flow may be of diagnostic value Disorders which produce hypertension with great frequency are pyelonephritis and glomerulonephritis The presence of hypertension is independent of the state of excretory function of the kidney.

CHAPTER XIV

HYPERTENSION OF POSSIBLE RENAL ORIGIN

We have just seen that a number of renal diseases may be associated with hypertension Such an etiologic factor, however, can be invoked in only a limited number of subjects In the majority of patients with hypertension, neither the history nor the usual examination reveals any renal damage. These patients are spoken of as having essential hypertension After it had been shown that hypertension could be produced experimentally by reducing blood flow to the kidney, a number of studies were made which suggested that the kidney plays an important rôle in the genesis of so-called essential hypertension We will review this evidence.

ESSENTIAL HYPERTENSION

By using the sphygmomanometric method of recording blood pressure in man, von Basch (1893) showed that there was a large group of patients in whom hypertension was the only manifestation of the disease Later studies by Albutt (1895) and Huchard (1899) defined the clinical entity known as essential hypertension According to Fishberg (1939), essential hypertension includes all those cases of chronic hypertension in whom neither clinically nor anatomically is there evidence of an antecedent inflammatory disorder of the kidney or urinary obstruction The term essential hypertension, as Fishberg points out, is a confession of our ignorance of the disease

Essential hypertension is the most frequent form of hypertension About 80 per cent of hypertensive individuals fall into this category The frequency with which essential hypertension is observed is apparently increasing progressively. This possibly depends on two factors: (1) the greater number of patients arriving at adult age, and (2) the high tension of living in our large cities. Considerable importance has been assigned to the latter factor. The clinical picture and course of essential hypertension are well known. A full and well documented study in this respect is to be found in the book by Fish-

berg (1939) and in the majority of monographs on diseases of the circulatory system.

From an etiologic and pathogenetic point of view, a number of factors have been considered to be responsible for essential hypertension Since a similar picture may be reproduced experimentally by reduction of blood flow to the kidney, many studies on the kidney have been performed on patients with essential hypertension A considerable body of anatomic evidence suggests, as we shall see, that this disease should probably be included in the group of hypertensions of renal origin

ANATOMIC EVIDENCE The kidneys of patients with essential hypertension show definite pathologic lesions in almost all cases Fahr in 1922 emphasized this point Fishberg (1925), in a study performed on 72 cases, found arteriosclerosis of the small arteries in all Bell and Clawson (1928) found changes of an arteriosclerotic type in 90 per cent of 420 patients with hypertension at autopsy These investigators pointed out the importance of sclerosis of the afferent arteriole of the glomerulus which showed changes in 89 4 per cent of the cases in contrast to its rarity in other diseases Moritz and Oldt (1937) observed arteriosclerosis of the renal vessels in 97 per cent of hypertensives and in only 12 per cent of patients with normal blood pressure (figure 91) Lesions observed in the hypertensive patients were in the majority of cases much more advanced than those observed in normal subjects In only 20 per cent of the normals was arteriosclerosis of the renal vessels comparable to that observed in the group of hypertensives These results have been confirmed by several other investigators.[1]

Vascular lesions of the kidney may consist simply of an arteriolosclerosis More frequently the sclerosis extends to the afferent arteriole of the glomerulus which in turn leads to changes in the glomeruli. In a more advanced stage, hyaline degeneration and glomerular atrophy appear As a result, the corresponding tubules undergo marked atrophy, the nephron finally being replaced by bands of connective tissue which extend to the renal capsule giving an ir-

[1] Williams and Harrison (1937), Oppenheimer, Klemperer and Moschkowitz (1939), Garreton-Silva, Rodríguez and Aspillaga (1941), Friedman, Moschkowitz and Marrus (1942); Lisa, Eckstein and Solomon (1943)

regular pitted appearance to the surface of this organ, from which the name red granular kidney is derived.

Histologically the lesions observed in the vessels in essential hypertension are characterized by endothelial hyperplasia, hyalinization of the intima, and changes in the media characterized by an increase in the muscular and elastic layers These changes depend on the size of the vessel and on the duration of the disease process.

Ischemia of Arteriosclerotic Origin.—Pathologic studies, therefore, frequently reveal arteriosclerosis of the renal vessels in the course of hypertension Vascular lesions produce parenchymatous changes which eventuate in the red granular kidney Let us consider the possibility that arteriosclerosis of the renal vessels is the cause of renal ischemia, and by this mechanism the cause of the hypertension

Three arguments are opposed to the hypothesis that hypertension is the result of ischemia produced by renal arteriosclerosis The first objection is that arteriosclerosis is a change appearing normally with age and that it may be present in the kidney without necessarily involving an elevation of blood pressure Cox and Dock (1941) perfused kidneys of human beings dying from various causes with kerosene and observed that the flow diminished with age as much in patients with hypertension as in those with normal blood pressure. It must be remembered, however, that the presence of renal arteriosclerosis in patients with normal blood pressure is much less than that observed in hypertensive individuals of an equal age, and it is of even greater importance that the lesions are much more advanced in the latter than in the former Furthermore, sclerotic lesions involve the afferent arteriole of the glomerulus with great frequency in essential hypertension (Bell and Clawson, 1928; Williams and Harrison, 1937), and this is probably a factor of considerable importance in the production of renal ischemia in occasional cases

The second objection against a renal arteriosclerotic origin of essential hypertension is that cases have been described in which no vascular lesions have been found Bell and Clawson (1928) and Garretón-Silva, Rodríguez and Aspillaga (1941) observed no changes in 10 per cent of their cases Pal (1919), von Monakow (1920), and Fishberg (1939) referred to isolated cases in which pathologic examination was negative. Castleman and Smithwick (1943), in a study performed on renal biopsies taken from 100 hypertensive patients during therapeutic splanchnicectomy, found that in more

than 50 per cent of the cases examined there were no vascular changes sufficiently pronounced to produce renal ischemia. They concluded that renal arteriosclerosis may be a possible factor aggravating hypertension but not causing it These conclusions must be accepted with some reserve, however, because as Scott (1944) has pointed out, renal biopsies give only limited information about the kidney as a whole

Although there is no doubt but that in certain patients with essential hypertension there are no demonstrable intrarenal vascular lesions, neither an ischemia of functional origin without pathologic changes nor an ischemia of arteriosclerotic origin can be ruled out as a cause for the hypertension in many of these cases Actually, as we have seen, lesions producing ischemia can be located in the trunk or at the mouth of the renal artery or even in the proximal part of the aorta (Blackman, 1939, Richardson, 1943) Such lesions may be overlooked in an incomplete examination

The third objection to the hypothesis that intrarenal vascular lesions are the cause of essential hypertension arises from the observation that an elevated blood pressure itself leads to arteriosclerosis Kirkes in 1855 observed this and it has subsequently been confirmed by a large number of investigators (Moschkowitz, 1942) It has furthermore been observed that hypertension, produced by a unilateral renal lesion, may lead to sclerosis of the vessels of the opposite kidney It has, therefore, been thought that the great frequency of renal arteriosclerosis may be the result rather than the cause of the hypertension A certain amount of evidence suggests that this is not the case Moritz and Oldt (1937), in their interesting study already mentioned, observed first that in hypertensive patients arteriosclerosis was much more frequent in the kidney than in other organs, secondly, that the difference and degree of arteriosclerosis observed in the kidneys of hypertensive and normal subjects of the same age was much greater than that observed in any other organs (figure 91)

We believe that the pathologic changes observed in the kidneys of patients with essential hypertension are of importance in its genesis because (1) renal ischemia has been shown to be intimately associated with the development of hypertension, (2) a parallelism exists between the severity of renal vascular lesions and the appearance and severity of hypertension in hypertensive patients, and (3) experimentally a clinical picture almost identical with that of essential

hypertension has been produced by partial constriction of the renal artery. It seems highly probable, therefore, that an ischemia is produced by the vascular lesions described, and that this ischemia is concerned in the genesis of essential hypertension.

RENAL FUNCTION For many years it has been considered that renal function in patients with essential hypertension is completely

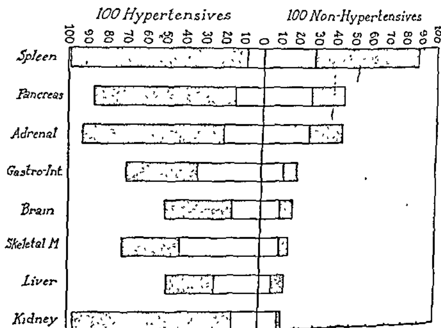


FIGURE 91 A COMPARISON OF THE OCCURRENCE OF ARTERIOLAR SCLEROSIS IN THE VARIOUS ORGANS AND TISSUES OF 100 HYPERTENSIVE AND 100 NON-HYPERTENSIVE INDIVIDUALS

Note that in all the organs moderate or severe arteriolosclerosis is more frequent in the hypertensives than in the normals, especially in the vessels of the kidney which are involved almost exclusively in the group with hypertension Stippled columns indicate advanced changes, white columns slight changes (After Moritz and Oldt, Am J Path, 1937, *13*, 679)

normal since the phenolsulfonphthalein test, urea clearance and Ambard's constant show no changes from the normal. Only in advanced cases is a diminution in the concentrating power of the kidney observed, as Dalton and Nuzum (1942) have recently emphasized An excellent review of the present status of renal function in hyper-

tension as indicated by clearance methods will be found in the book by Goldring and Chasis (1944)

Renal Blood Flow.—After the introduction of special techniques, it was shown that the kidney of hypertensive patients, despite maintaining sufficient excretory function to prevent nitrogen retention, developed functional changes of considerable interest as regards its rôle in the production of hypertension

From the relationship of glomerular filtration (C_i) and renal plasma flow (C_D) to tubular excretory mass (Tm_D) (see Chapter II), considerable information has been obtained with regard to renal function in patients with essential hypertension Chesley and Chesley (1940) found a diminution of blood flow and increase of glomerular filtration in women with essential hypertension Goldring, Chasis, Ranges and Smith (1941), in a meticulous study of 60 patients with essential hypertension, found a diminished capacity to excrete diodrast in all patients This became progressively reduced as the disease advanced Simultaneously they observed a diminution of renal blood flow per unit of functional excretory tissue associated with an increase of glomerular filtration Both groups of observations were in agreement in that they showed an increase of pressure in the glomerulus and a diminution of renal blood flow. This increase of pressure in the glomerulus with diminution of blood flow has been attributed to a constriction of the efferent glomerular arteriole The same investigators found that the injection of pyrogenic substances reduced glomerular filtration indicating that constriction of the efferent vessel was reversible In many of their cases, a simultaneous increase of Tm_D was observed, which according to these authors indicated that some tubules may have been inactive due to ischemia. These results were confirmed by Friedman, Selzer and Rosenblum (1941), and by Foà, Woods, Peet and Foà (1942a, b, 1943) In studying 20 hypertensive patients, these investigators also found a reduction of renal blood flow which apparently bore a relation to the severity of the disease as indicated by eyeground changes and by changes in the appearance of the arterioles

The investigations mentioned indicate that the increase of glomerular filtration guarantees a normal elimination of urea and therefore a normal concentration of urea in the blood. Ischemia of the tubules, on the other hand, rapidly interferes with their function, thereby causing an early diminution in the ability of these patients

to concentrate urine In the majority of hypertensive patients studied by clearance methods, a more or less marked renal ischemia exists This does not prove that this change is the cause of the hyper tension, however, since it is not known whether the reduction of blood flow is preceded or followed by the hypertension.

Friedman, Selzer and Rosenblum (1941) believed that reduction of renal blood flow might be an expression of generalized vasoconstriction They considered that the functional change for maintaining glomerular filtration was an aggravating rather than a primary etiologic factor.

Chasis and Redish (1941, 1942) studied the function of both kidneys separately in 20 hypertensive patients and found that progressive tubular destruction and functional changes occurred to the same extent on both sides. These authors believed that this evidence excluded an ischemic origin since it would be expected that there would be differences in the degree of change between the two kidneys Steinitz (1941) found no reduction of renal blood flow in 4 of 6 patients with essential hypertension, which agrees with the results recently published by Findley, Edwards, Clinton and White (1942)

Friedman, Selzer, Kreutzmann and Sampson (1942) observed that in 3 hypertensive patients with unilateral renal lesions, nephrectomy did not lower the blood pressure despite the fact that the renal blood flow of the remaining kidney was normal.

Recently Talbott, Castleman, Smithwick, Melville and Pecora (1943) compared the anatomic with the functional state of the kidney in hypertensive patients by means of biopsies obtained during operation They observed that reduction of blood flow bore a relation to the severity of the vascular lesions Contrary to the results obtained by Goldring, Chasis, Ranges and Smith (1940, 1941), these investigators did not observe an increase in the filtration fraction in cases with minimal vascular changes which suggested that constriction of the efferent vessel did not exist in the early stages of the disease.

Although these results offer serious objection to acceptance of the hypothesis that the immediate cause of the production of hypertension is renal ischemia, we believe that they can not be considered as final proofs. While the studies of Friedman, Selzer and Rosenblum (1941) and those of Chasis and Redish (1941, 1942) raise doubts as to the existence of a primary renal ischemia of organic origin, it is still possible that there is an ischemia of functional origin conditioned

by some cause as yet unknown. As regards the observations of Friedman, Selzer, Kreutzmann and Sampson (1942), it is difficult to know whether halving the figure accepted for renal blood flow under normal conditions with both kidneys intact can be extended to cases in which only one kidney must accomplish the total excretory function. As regards the results obtained by Talbott, Castleman, Smithwick, Melville and Pecora (1943), there was a fairly good correlation between the severity of the vascular lesions and renal blood flow as well as an excellent correlation between blood flow and the height of the blood pressure. Only in those cases in which the blood pressure showed insignificant rises was the renal blood flow normal Finally, the results obtained by Steinitz must be considered as of limited significance since the number of cases studied was small, and those of Findley, Edwards, Clinton and White, as the authors themselves admitted, had the defect that renal blood flow was not correlated with functional tubular mass

The experimental injection of hypertensin and renin in man produces changes in renal function (see Chapters IV and VI) which are identical with those observed by the majority of investigators mentioned in patients with essential hypertension

In summary, it may be concluded that the majority of measurements of renal blood flow in hypertensive individuals by the clearance methods appear to demonstrate the existence of a certain degree of renal ischemia in essential hypertension From the evidence presented, it seems to us that the hypothesis that best fits the known facts is that the immediate cause of essential hypertension is related to renal ischemia and, with certain reservations (see Chapter XVIII), that renin and hypertensin are probably the substances which cause the blood pressure to rise

MALIGNANT HYPERTENSION

In certain individuals, hypertension is severe and its course is rapid. Volhard and Fahr (1914) were the first to recognize this malignant type of hypertension from the clinical and pathologic point of view and believed it to result from an association of a glomerulonephritic process with a pre-existing arteriosclerosis They considered it to be a combined form of hypertension. Other names were subsequently proposed for this type of hypertension Fahr (1919) from anatomic studies called it malignant sclerosis, Volhard (1923), pale

hypertension; Keith, Wagener and Kernohan (1928), syndrome of malignant hypertension, and Fishberg (1939) malignant phase of essential hypertension. The clinical picture of malignant hypertension is well known and is characterized by the presence of generalized manifestations: Anorexia, loss of weight, weakness; cerebral symptoms such as headaches, nausea, vomiting, convulsions, elevated cerebro-spinal fluid pressure, ocular signs, changes of vision, edema of the discs, sclerosis of retinal vessels, hemorrhages and exudates in the eyegrounds, vascular symptoms and signs, marked elevation of systolic and diastolic pressure, cardiac hypertrophy with frequent pericarditis, and finally a picture of renal insufficiency as indicated by albuminuria, hematuria, hyposthenuria, and nitrogen retention leading to uremia which is the most frequent cause of death in these individuals

The clinical picture is typically accompanied by a pathologic picture characterized by arteriolar necrosis and endarteritic thickening of the intima This arteriolar process was first demonstrated by Fahr (1919) in the kidney and later confirmed by Herxheimer (1924) and by Stern (1924).

Necrotizing arteriolitis, although encountered mainly in the kidney, is also observed in the retina, intestine, liver, adrenal capsule, pancreas, striated muscles and so forth. It is therefore a generalized arteriolar process as Volhard (1923) first pointed out and as many others have later confirmed (Keith, Wagener and Kernohan, 1928; Murphy and Grill, 1930, Fishberg and Oppenheimer, 1930; Wagener, 1930; Ellis, 1938; and others).

ETIOLOGY A variety of etiologic factors have been assigned to malignant hypertension We have already stated that Volhard and Fahr (1914) considered it to be the result of the association of a glomerulonephritis with a pre-existing arteriosclerosis. Fahr (1919) subsequently considered that malignant hypertension was the result of toxic or infectious processes which led to arteriolonecrosis. Most authorities believe, however, that malignant hypertension is a rapidly progressive form of essential hypertension. In support of this, Fishberg (1939) gives the following reasons: (1) In a large proportion of cases malignant hypertension appears after many years of an asymptomatic essential hypertension (2) Autopsy reveals, along with the changes typical of malignant hypertension, kidneys with arterio-

sclerosis of long duration with hyalinization of the glomeruli and other lesions which have been found in almost all cases of essential hypertension. (3) The family history of the majority of patients with malignant hypertension reveals that other members of the family have died of essential hypertension. About 10 per cent of patients with essential hypertension die of malignant hypertension. In some cases, however, malignant hypertension follows or is a result of a hypertensive syndrome of well defined etiology and therefore separable from essential hypertension Derow and Altschule, in 1935, called attention to this fact and considered malignant hypertension to be not an independent disease but rather a syndrome in which the hypertension is primary (essential) or secondary to other diseases. This opinion was subsequently accepted implicitly or explicitly by Page (1939e), Kimmelstiel and Wilson (1936a, c), Williams and Harrison (1939), Weiss and Parker (1939), Wilson and Byrom (1939), and others Derow and Altschule (1941) more recently expressed the opinion from data collected from the literature that malignant hypertension may be the result of a series of well defined etiological factors as follows·

- I. Essential or primary hypertension
- II Secondary hypertension
  - A. Renal disease
    - 1 Glomerulonephritis
    - 2 Pyelonephritis
    - 3 Intercapillary glomerulosclerosis
    - 4 Unilateral congenital hypoplasia
    - 5 Obstruction of the renal artery by an arteriosclerotic plaque
    - 6 Multiple occlusions of small renal arteries
    - 7 Renal infarct
    - 8 Periarteritis nodosa of the renal vessels
  - B Lead poisoning
  - C Endocrine diseases
    - 1 Pituitary basophil adenoma
    - 2. Adrenal hypernephroma, paraganglionoma
    - 3 Hypertension of pregnancy

PATHOGENESIS Despite a certain amount of knowledge concerning etiologic factors, the mechanism by which malignant hyper-

tension appears is still unknown. Volhard (1923) believed that malignant hypertension (pale hypertension) was due to the presence of vasoconstrictor substances in the blood which produce a generalized vasoconstriction capable of producing ischemic manifestations with vascular changes in the kidney, retina, and other organs

In Chapter II, the experimental production of malignant hypertension by Goldblatt and his collaborators was discussed, from which it was concluded that malignant hypertension is the result of a combination of severe hypertension, a greater or lesser degree of renal insufficiency, and tissue autolysis. There is evidence that the hypertension itself is of importance in the production of vascular changes in the malignant stage of hypertension in man. Fishberg (1939), for example, observed that patients with essential hypertension who develop a malignant stage have a more or less prolonged period previously in which the systolic and especially the diastolic pressure is extremely elevated. Furthermore, there are a series of reported cases in which malignant hypertension has developed as a result of unilateral renal disease and in which pathologic lesions typical of malignant hypertension are found only in the opposite kidney in which the circulation is not affected. Under these circumstances, the vessels are submitted to the increase of pressure. Saphir and Ballinger (1940) described the case of a 35-year-old woman who had an atrophic pyelonephritis on one side and malignant lesions on the other, and of a 46-year-old man with an organized thrombus in the left renal artery and arteriolonecrosis of the right kidney. Similar cases have been reported by Laas (1940), Davson (1941), and others cited in Chapter XIII.

If would therefore appear that in man the association of hypertension and renal insufficiency may be the possible cause of malignant hypertension. Cases have been described, however, in which malignant hypertension has appeared in the absence of any manifestation of renal insufficiency (Keith, Wagener and Kernohan, 1928; Murphy and Grill, 1930; Leiter, 1938; and others). The etiologic cause in these cases is difficult to define. It should be noted, however, that Winternitz, Mylon, Waters and Katzenstein (1940) observed that the injection of extracts of various tissues into nephrectomized animals produced vascular changes and arteriolonecrosis similar to those observed in malignant hypertension In human beings with long standing hypertension, it is possible that vascular sclerosis

secondary to hypertension or to functional changes of a spastic type are capable of creating an ischemia and necrosis in different parts of the body which would secondarily lead to the establishment of malignant hypertension. We have had the opportunity of observing a case which is possibly illustrative of this point This was a hypertensive patient who after myocardial infarction developed a mesenteric embolus and typical malignant changes in the eyegrounds and associated phenomena of arteriolocapillaritis This point is still not clear and deserves further study.

Many studies have been made on the relation of renal ischemia to essential hypertension

Pathologic studies have revealed sclerosis of renal vessels in approximately 90 per cent of autopsies on patients with hypertension This renal arteriosclerosis characteristically involves the afferent glomerular arteriole. In hypertension, the degree of vascular sclerosis is much greater in the kidney than in other parts of the body and is much more extensive in hypertensives than in those of a similar age who have no hypertension From the literature, it would appear that many hypertensive patients have lesions in the main trunk of the renal artery or at its mouth That such lesions are a frequent cause of renal ischemia seems doubtful

Hypertension may exist without demonstrable lesions of the intrarenal vessels Studies of the main trunk of the renal artery have not been made in these cases so that it is not possible to exclude absolutely the existence of ischemia Studies of the vascular system of the kidney would profitably include an examination of the renal artery from its mouth as far as the afferent arteriole of the glomerulus in order to prove that there are cases of hypertension without vascular abnormalities

The over-all excretory function of the kidney is usually normal. Renal blood flow in the majority of cases is reduced This reduction apparently bears some relation to the degree of hypertension, is bilateral, and is equally divided between the two kidneys It is not clear whether this reduction of blood flow depends on the vascular lesions already mentioned, or whether they are due to vasospastic phenomena from functional derangements of the kidney, primary or secondary to processes initiated in other parts of the body This is an

important point which remains to be elucidated, and would necessitate a combined functional and anatomic study on hypertensives followed over a long period It is our belief that the hypothesis which at this time best fits the known facts is that the immediate cause of essential hypertension is related to renal ischemia despite certain important evidence to the contrary.

Malignant hypertension often follows a pre-existing essential hypertension, but frequently is found in association with hypertension of known etiology such as renal diseases, endocrine disorders, and the like. Hypertension and renal insufficiency are concerned in its production in the majority of cases Renal insufficiency, however, may be lacking. In these cases, the malignant hypertension is possibly a result of the appearance of areas of necrosis produced by vascular changes of sclerotic or spastic origin.

CHAPTER XV

MECHANISM OF RENAL HYPERTENSION IN MAN

Blood pressure is determined largely by the resistance [illegible] the vascular system to the passage of blood pumped by the [illegible] the vascular system remains unchanged, the pressure may [illegible] result of change in the amount of blood which *circulates* [illegible] time (cardiac output per minute) or of the total quantity [illegible] ing blood (blood volume), or, finally, of the viscosity of [illegible]

BLOOD FACTORS

CARDIAC OUTPUT Increase of minute volume [illegible] heart has been considered to be one of the possible causes [illegible] tension As Fishberg (1939) pointed out, Bright referred to [illegible] nism in speaking of conditions of the blood which [illegible] work of the heart Several investigators have found an [illegible] minute volume output in hypertension Hayasaka [illegible] triple extrapolation method found it to be increased 50 [illegible] furthermore observed a certain proportionality between [illegible] of blood pressure and the increase of minute volume [illegible] *and Weiss (1929)*, Liljestrand and Stenström (1925), [illegible] (1930) also found variable increases in the minute [illegible] of the heart in essential hypertension Some investigators, [illegible] (Lauter and Baumann, 1928, and Ewig and Hinsberg, [illegible] found a reduction Extensive studies with more accur[illegible] performed by Burwell and Smith (1929), Grassmann [illegible] (1931), Ringer and Altschule (1930), and Weiss and Ellis [illegible] shown that in hypertensive patients under basal circul[illegible] tions, the minute volume output is within normal lim[illegible]

BLOOD VOLUME Increase of blood volume has also be[illegible]

(1927) observed no important changes in blood volume in patients with different types of hypertension Gibson and Harris (1939) also found no appreciable changes in essential hypertension In hypertensive patients with glomerulonephritis, they usually found a decreased blood volume as compared with the normal, mainly due to a diminution in the red cell volume, the plasma volume remaining unchanged or slightly increased.

Recently, Gazmuri-Ojeda and Denegri (1942), using trypan red, found a diminution of blood volume in hypertension without cardiac insufficiency.

BLOOD VISCOSITY. Increase of blood viscosity is another factor which has been considered as a possible cause of hypertension in plethoric individuals. In support of this, some investigators have found an increase in viscosity in this type of hypertension (Harris and McLoughlin, 1930) Austrian (1911), on the other hand, and more recently Pickering (1939) found a normal blood viscosity in subjects with essential hypertension while it was usually diminished in nephritis in which in addition to hypertension there was a certain degree of anemia.

Other clinical evidence tends to exclude the participation of these factors in the production and maintenance of hypertension Marked changes in minute volume output, blood volume and viscosity occur in such conditions as hemorrhage, exercise, polycythemia and pregnancy without producing consistent or uniform changes in blood pressure It may be concluded, therefore, that hypertension is not due to physical changes of the circulating blood.

VASCULAR FACTORS

Causes of hypertension must, therefore, be sought in other factors which are concerned with the regulation of blood pressure, i e. the vascular system. Loss of elasticity as well as diminution in the calibre of blood vessels are capable of producing changes of blood pressure.

LOSS OF ARTERIAL ELASTICITY by sclerosis is a normal phenomenon as the arterial system ages. In many patients, however, it appears at an early age in accentuated form. Normally the blood expelled during systole remains in the aorta and large vessels thanks to their elasticity. After ventricular systole finishes, the continuous

flow of blood is maintained through the elastic properties of the large vessels The vascular elasticity dampens the systolic rise and maintains the mean and diastolic pressures which are responsible for the continuous and effective flow of blood.

Loss of elasticity of the aorta and great vessels causes an increase of systolic pressure and a fall of diastolic pressure. Although this systolic hypertension of arteriosclerosis is common, its mechanism, symptomatology and course are different from that of patients included in the group which we are studying There is no doubt, however, but that arteriosclerosis of the large vessels is present in the majority of cases of chronic hypertension and can accentuate the elevation of the systolic pressure by the mechanism described

In summary it may be said that loss of elasticity may produce an isolated systolic hypertension or produce an increase in pulse pressure in chronic hypertension (Weiss, Haynes and Shore, 1936), but elevation of both systolic and diastolic pressure is due only to an increase of peripheral resistance resulting from reduction in the calibre of the vessels.

PERIPHERAL RESISTANCE Prinzmetal and Oppenheimer (1937), studying the blood pressure in arteries of different size in hypertensive subjects, observed that the fall of pressure in the large and small arteries was the same as that observed in normal subjects From this they concluded that there was no increase of resistance in the arteries studied and concluded that the hypertension was due to an increase in the resistance of vessels smaller than the digital artery

Wiggers (1938) believed that the resistance offered by arterioles was the fundamental process but was not the only one The increase of pulse pressure observed in the majority of hypertensives was due, he believed, to a diminution in the elasticity of the vessels of large calibre This point deserves further study

For many years it has been hypothesized that hypertension might be due to localized vasoconstriction in the splanchnic region If this were so, there would be an irregular distribution of blood which would be shunted in large part to the sites of lower resistance This should produce a partial functional deficit in areas ischemic from vasoconstriction and signs of congestion in other areas such as the skin and the limbs Abramson and Fierst (1942) recently obtained evidence that would appear to support the hypothesis of an irregular

distribution of peripheral resistance in hypertension. Ellis and Weiss (1929) showed that there was an increase of arteriolar pressure in the sternal region, and Steele and Kirk (1934) found that skin temperature, registered at different times of day and in different parts of the body, was the same in normal as in hypertensive individuals. Prinzmetal and Wilson (1936) and Pickering (1936b) independently and almost simultaneously found that blood flow in the forearm was the same in normal subjects as in patients with benign or malignant essential hypertension and nephritis These investigations were confirmed by *Stead and Kunkel (1940)* who extended the study to other parts of the body such as muscles and brain with the same results These studies indicated a uniform distribution of peripheral resistance and an equilibrium between the resistance and increase of blood pressure so that normal blood flow was found in the various organs of the body.

An increase of peripheral resistance localized preferentially to the small precapillary vessels (Eichna and Bordley, 1941) may depend on an anatomic change of the vessels or on a functional change (vaso*constriction*)

Anatomic Causes —Kirkes in 1855 described a generalized arteriosclerosis in hypertension. Gull and Sutton (1872) attributed the hypertension to an increase of resistance produced by an anatomic change of the vessels, a theory which has the support of other investigators.

Doubt has been thrown on this factor by a large number of experiments Pickering (1936b), Prinzmetal and Wilson (1936) and Stead and Kunkel (1940) demonstrated that the reactive capacity of the vascular system to different agents was the same in hypertensive as in normal subjects Stead and Kunkel (1940) observed no change in blood flow in one case in which a pronounced and maintained fall of pressure had been induced by malaria In another case, however, they found the fall of blood pressure to be accompanied *by a diminution* of blood flow. From this result, which was identical with observations made by Wilkins and Eichna *(1940)* on *hypertensives* after sympathectomy, the authors concluded that structural lesions had developed *as a result of active pre-existing* vasoconstriction.

Burch, Cohn and Neumann (1941) found the reactivity of the vessels of the fingers of hypertensive subjects to be intact in response to

different stimuli, while it was diminished in patients with senile arteriosclerosis. Di Palma and Foster (1942) observed the small vessels of the forearm to have the same sensitivity in hypertensives as in normals.

It may be concluded that the reactivity of the vessels is normal according to the experiments discussed above, which is in contradistinction to that which is observed in arteriosclerosis There is little evidence to indicate an organic alteration of the vessels in hypertension The only possible cause for hypertension therefore is a generalized vasoconstriction. This vasoconstriction may depend on two mechanisms—nervous or humoral.

Neurogenic Causes—Many investigators believe that hypertension is due to a *neurovegetative imbalance* with a predominance of the sympathetic system. Since hypertension can be produced experimentally by section of the pressor receptor nerves as we have discussed in Chapter I, it has been thought that a possible cause of human hypertension is a decreased sensitivity of these areas (Koch, 1929, Mies, 1932) Gammon (1936) showed that the response of the carotid sinus to changes of pressure in hypertensive patients was normal. Weiss and Baker (1933) also showed that in various types of hypertension the function of the carotid sinus was the same as in normal individuals Prinzmetal and Wilson (1936) and Pickering (1936b) demonstrated that sympathetic paralysis induced by novocaine or applications of local or general heat produced an equal increase of blood flow of the arm in hypertensive and normal subjects They also showed that reactive hyperemia was the same in both groups

Stead and Kunkel (1940) gave new support to these conclusions They investigated changes of blood flow produced by different physical and chemical stimuli in the arm, leg, muscle of the forearm, and brain Despite differences in distribution of nerves to the areas investigated, changes of blood flow observed were similar in all.

These investigations, the failure of surgical treatment in many cases of hypertension, and experimental evidence all tend to exclude vasoconstriction of nervous origin as a fundamental mechanism of human hypertension It must be assumed, therefore, that hypertension is due to a vasoconstriction maintained through a humoral mechanism.

Humoral Causes—Many of the older theories explained hyper-

tension by retention of toxic substances not well defined (Bright, 1836; Johnson, 1868) Many attempts were subsequently made to demonstrate the presence of vasoconstrictor or pressor substances in the blood of hypertensive patients. Broking and Trendelenburg (1911) found no greater vasoconstrictor action on the vascular system of the frog from blood of hypertensives than from that of normal individuals, which was confirmed years later by Hulse (1922) Stewart in 1911 investigated the pressor action of blood by the injection of small amounts of serum from hypertensive patients into dogs with negative results.

Similarly negative results were obtained by Danzer, Brody and Miles (1926) and Hulse (1929) with injections of blood of hypertensives into cats, and Curtis, Moncrieff and Wright (1927) and Hülse (1929) by injections into dogs. Danzer (1927), however, found that the blood of some hypertensives injected into cats caused rises of pressure of from one to two minutes' duration which was not observed with normal blood. Volhard (1931) supported the theory of a humoral mechanism by considering that pale hypertension was due to the liberation of pressor substances His disciple, Bohn, in 1932, found that alcoholic extracts of blood and urine of patients with malignant hypertension had a pressor action in cats which was much greater than that observed with extracts of blood from other types of hypertension and from normal subjects Marx and Hefke (1933) also observed a pressor action in unanesthetized dogs from the injection of extracts equivalent to 80 to 100 cc. of blood, and Westphal and Sievert (1938a, b) found a pressor action in the ultrafiltrate of blood from essential hypertensives. Elliot and Nuzum (1933), on the other hand, found that in rabbits the response to injections of blood from normals and hypertensives was the same. deWesselow and Griffiths (1934) did not find any difference in pressor action from the injection of extracts of blood from malignant hypertensives and normal individuals Bohn and Schlapp (1932, 1935) confirmed the presence of pressor substances in malignant hypertension and attributed the negative results previously reported to defects in technique.

The existence of specific pressor substances in essential hypertension has been denied by the more recent investigations of Wakerlin and Bruner (1933), Capps, Ferris, Taylor and Weiss (1934), Page (1934b), Aitken and Wilson (1935) and Leiter (1936) Page (1940e),

using the isolated rabbit's ear, and Garreton-Silva, Croxatto, Fuenzalida and Viveros (1941), using the Läwen-Trendelenburg preparation found that the plasma from patients with different types of hypertension possessed a vasoconstrictor action Page (1945) has more recently described the presence of vasoconstrictor substances in the citrated plasma of animals and patients with hypertension as indicated by a constrictor action in the isolated rabbit's ear This substance had to be "activated" by another substance contained in the ultrafiltrate of normal plasma before its constrictor action became apparent These results have not been confirmed by Landis (1944) using the rabbit's ear preparation, nor have we been able to confirm the observations of Garreton-Silva and collaborators using the Läwen-Trendelenburg preparation The positive results obtained by Page and Garreton-Silva and co-workers are best attributed to vasoconstrictor substances appearing in shed blood (see Chapter XI). The rabbit's ear method is particularly subject to large constrictor artifacts both from histamine and from substances produced by disruption of platelets (Landis, Wood and Guerrant, 1943, Landis, 1944; and Landis, Thomas and Wood, 1945)

The blood of hypertensive patients has also been investigated for pressor activity by means of direct transfusion from man to man. Host (1931) was the first to carry out such experiments and his results were negative. Pickering (1936a) found no difference in pressor effect of transfusions of 350 to 600 cc of blood from hypertensives and from normal subjects Prinzmetal, Friedman and Rosenthal (1936) likewise observed no elevation of blood pressure in patients with a normal circulatory system after the transfusion of 500, 700, 1,460 and 2,000 cc of blood from patients with malignant hypertension despite having effected an interchange of 45 per cent of the total blood volume.

From the large number of investigations discussed, it may be concluded that hypertension is due to an increase of peripheral resistance by arteriolar vasoconstriction This vasoconstriction may be humoral in origin although the pressor substance has not been identified in the systemic blood Since hypertensin injected into man produces circulatory changes similar to those observed in hypertension (see Chapter VI), it is possible that this substance is the responsible agent. Although neither hypertensin or renin can be detected in the

blood, this may be due to their presence in such small quantities that they can not be recovered by techniques available at this time or to other factors which are discussed in Chapter XVIII

The minute volume output of the heart, blood volume and blood viscosity are normal in patients with hypertension and can not, therefore, be considered to be concerned with the production of hypertension Since hypertension does not depend on factors in the blood, it must be attributed to an increase in peripheral resistance of the vascular system The uniform distribution of skin temperature and the lack of change of peripheral blood flow in different parts of the body indicate that the distribution of blood is not altered in hypertensive subjects It may be concluded, therefore, that hypertension is not due to an increase of vascular resistance which is localized in some area such as the splanchnic region Studies of blood pressure in the large and small arteries and the lack of change of capillary pressure show that the generalized increase of resistance producing the hypertension is located in the arterioles

The normal reaction of vessels to different chemical or physical excitants indicates that this increase of peripheral resistance is not due to an organic change in the arterioles but rather to a generalized vasoconstriction

Anesthesia of the sympathetic nervous system does not alter blood pressure in hypertension, and different vascular areas of the body react to different stimuli as do normal patients despite the fact that sympathetic activity is not the same in every patient. These observations indicate that the arteriolar vasoconstriction is not of nervous origin

Hypertension must be due then to an arteriolar vasoconstriction of humoral origin. Search for pressor and vasoconstrictor substances in the blood of hypertensive patients has given negative results up to this moment

It is possible that hypertensin, which produces circulatory changes similar to those found in hypertension, is the responsible agent Further study and experimentation will be required to elucidate this point.

CHAPTER XVI

MEDICAL TREATMENT OF HYPERTENSION OF RENAL ORIGIN

It is not our purpose to review in this chapter the many medications which have been proposed for the treatment of different clinical types of human hypertension In this book we have restricted ourselves to the problem of experimental renal hypertension Therefore, we will consider only (a) attempts at nonspecific treatment, and (b) attempts at specific treatment of experimental and human hypertension, making the assumption that human hypertension is of renal origin

We recognize the limitation of our restrictions Although there is a close similarity between experimental renal hypertension and human essential hypertension, there are certain fundamental differences. Thus as human diabetes is not entirely identical with the diabetes of a pancreatectomized animal, human hypertension likewise is not identical with experimental hypertension Human hypertension is unstable, especially at its onset, since it may disappear with bed rest and sedative treatment or with dietary or psychotherapeutic measures. In many cases of human essential hypertension, the administration of hypnotics, narcotics or anesthetics produce a profound fall of blood pressure, these being the most favorable cases for surgical sympathectomy In dogs with experimental hypertension, the injection of anesthetics or hypnotics does not cause the pressure to fall significantly unless there is a co-existent psychogenic factor (Goldblatt, Kahn and Lewis, 1942)

As regards pathologic changes, there is also a fundamental difference between both forms of hypertension In the experimental disorder there is a change of renal circulation resulting from constriction of the renal artery or compression of the kidney. In essential hypertension it is believed at this time that there is from the beginning a certain degree of arteriolar sclerosis which affects the small intrarenal arteries, especially the preglomerular arterioles

Recognizing these differences and assuming that experimental

TABLE V

Substance Employed	Animal	Daily Dose	Route of Administration	Period of Treatment Days	Effects on Blood Pressure
Nitrites and Nitrates					
Erythrol tetranitrate[1]	Rat	0.03 gm.	Oral	5	None
Erythrol tetranitrate[1]	Rat	0.06 gm.	Oral	5	Moderate fall
Erythrol tetranitrate[2]	Rat	0.05 gm	Oral	7	None
Mannitol hexanitrate[3]	Dog	0.08 gm.	Oral	21	None
Bismuth subnitrate[2]	Rat	0.075 gm.	Oral	8	None
Sodium nitrite[1]	Rat	0.1 gm	Oral	5	None
Sodium nitrite[1]	Rat	0.2 gm	Oral	5	Moderate fall
Sulfocyanates					
Potassium sulfocyanate[4]	Dog		I V		Fall
Potassium sulfocyanate[1]	Rat	0.1 gm.	Oral	5	None
Potassium sulfocyanate[1]	Rat	0.2 gm.	Oral	5	Moderate fall
Potassium sulfocyanate[2]	Rat	0.1 gm.	Oral	7	None
Potassium sulfocyanate[2]	Rat	0.2 gm	Oral	7	Moderate fall
Potassium sulfocyanate[2]	Dog				Moderate fall and toxic symptoms
Magnesium salts					
Magnesium carbonate[2]	Rat	0.2 gm.	Oral	10	None
Magnesium sulfate[2]	Rat	0.05 gm	Oral	6	None
Choline salts					
Choline chloride[3]	Dog	5.2 gm.	Oral	21	None
Acetylcholine[5]	Dog	2–5 mgm.	I.V.	44	None
Acetyl-methyl choline hydrochloride[1]	Rat	0.5 mgm.	S.C.	5	None
Acetyl-methyl choline hydrochloride[1]	Rat	1.0 mgm.	S.C.	5	Moderate fall
Bromides					
Sodium bromide[3]	Dog	8.0 gm	Oral	10	None
Vegetable Extracts					
Allium sativum (garlic)[5]	Dog	2.0 gm	Oral	60	None
Allium sativum (garlic)[1]	Rat	1.0 gm	Oral	5	None
Allium sativum (garlic)[2]	Rat	0.5–1 mgm	Oral	8	None
Allium sativum (garlic)[3]	Dog	0.6 cc	Oral	15	None
Viscum album (mistletoe)[3]	Dog	0.2 gm	Oral	15	None
Veratrum viride (tincture)[3]	Dog	1–2 cc.	Oral	15	None
Watermelon seed[3]	Dog				None
Vitamins					
Vitamin A[6,7]	Dog	200,000 to 400,000 U	Oral	90–180	Definite fall
Nicotinic acid[3]	Dog	0.2–2.0 gm	Oral	21	None
Biotin[3]	Dog	1,000 U	S.C.	10	None
Vitamin B*[7]	Dog	8–12 cc.	Oral	42	None
Ascorbic acid[7]	Dog	1.0 gm.	Oral	120	None
Vitamin E[7]	Dog	100 mgm	Oral	150	None

TABLE V—*Continued*

Substance *Employed*	Animal	Daily Dose	Route of Administration	Period of Treatment Days	Effects on Blood Pressure
Tissue Extracts					
Pancreas (powdered)[4]	Dog	0 3 gm.	Oral	30	None
Pancreas (powdered)[2]	Dog				None
Adrenal cortex[4]	Dog	0 1 cc /kgm	S C.	30	None
Liver[4]	Dog	6–12 cc	I V and I M	30	None
Pituitary[3]	Dog	1 5 gm /kgm	I.M.	30	None
Hormones					
Estrone[6]	Dog	0 1 mgm /kgm	I M	30	None
Testosterone[6]	Dog	2 5 mgm /kgm.	I M	30	None
Pituitrin[5]	Dog	10 U/kgm	I M.	15	None

[illegible] flavin, 0 15 mgm pyridoxine, 2 [illegible]
[illegible] lin, Moss and Smith (1942)
[illegible] and Wakerlin (1944)
[illegible] ravenously
[illegible] ramuscularly
[illegible] cutaneously

hypertension is an example rather than an imitation of the human disease, we believe that there is today no more fertile lead for the discovery of specific and effective therapy for essential hypertension than study of the response of hypertensive animals to therapeutic measures Empiricism is thereby supplanted by experimental investigation

EFFECT OF VARIOUS THERAPEUTIC AGENTS ON BLOOD PRESSURE

In table 5 may be seen the results obtained by several investigators from the administration of a number of therapeutic substances to animals with hypertension from renal ischemia. In a recent article in which different drugs proposed for the treatment of human hypertension were reviewed, Mosenthal (1940) came to the conclusion that there were no means by which an elevated blood pressure could be appreciably and consistently lowered

Of the drugs which appear in the table, we will mention only those which have produced some effect With erythrol tetranitrate and with sodium nitrite, Grollman, Harrison and Williams (1940a) obtained a slight fall of pressure in hypertensive rats Goldblatt,

Kahn and Lewis (1942), however, observed no effect from mannitol hexanitrate in hypertensive dogs Grollman, Harrison and Williams (1940a) claimed to have observed slight falls in rats by the administration of 1 mgm of acetyl-beta-methylcholine hydrochloride daily. Goldblatt, Kahn and Lewis (1942) obtained no effect from the administration of 2 to 5 mgm. per kgm of acetylcholine per day or up to 5 2 gm. of choline chloride daily to hypertensive dogs.

The present status of thiocyanates in the treatment of hypertension has recently been reviewed by Forster (1943) who concluded that although the majority of authors are in favor of its use, a small number of careful observers believe that its effectiveness has not been demonstrated and that its use is not without danger. Its dangers may be largely but not entirely averted by governing dosage by maintaining the blood level at approximately 8 to 10 mgm per cent. Forster pointed out that none of the clinical reports have completely eliminated all the variables which might cause unrelated reductions of blood pressure Goldblatt, Kahn and Lewis (1942) observed no decline of blood pressure in hypertensive dogs receiving thiocyanates until such a high dosage was given that toxic symptoms appeared, the depressor effect being preceded by anorexia, vomiting and at times diarrhea. Davis and Barker (1941) found that hypertensive dogs and human beings were made more sensitive to the action of sulfocyanate by splanchnicectomy. Grollman, Harrison and Williams (1940a) also considered that the reduction of blood pressure which they obtained with nitrites, sulfocyanates and acetylcholine was due more to a "toxic" effect than to a "hypotensive" effect since the smallest reductions were accompanied by apathy and anorexia and if the dose was increased the animals died.

Govea-Peña and Villaverde (1940) reported favorable results in the treatment of essential hypertension in man by large doses of vitamin A by mouth These observations, which were not confirmed by Corcoran (1943), Blumenthal and Wetherby (1943), Dexter, Bridges and Quinby (personal communication), and others, induced Wakerlin, Moss and Smith (1942) to use concentrates of vitamin A for the treatment of experimental hypertension. These authors submitted three hypertensive dogs to a treatment consisting of the oral administration daily of 200,000 units of vitamin A for three months and 400,000 for another three, and observed noteworthy falls of blood pressure in the three animals. Two control hypertensive dogs

received a daily equivalent amount of the solvent (1 to 2 cc. of sesame oil) without the blood pressure undergoing any change

Since more purified preparations of vitamin A had no action (Moss, Smith and Wakerlin, 1943, Wakerlin, Johnson, Moss and Smith, 1943, Wakerlin and Moss, 1943, Moss and Wakerlin, 1944; Katz, Rodbard and Meyer, 1943) and since preparations in which vitamin A was previously destroyed by heat (Moss, Smith and Wakerlin, 1943), by irradiation with ultraviolet light or by oxidation (Grollman and Harrison, 1943a, b) were equally active or even increased in activity, the depressor action of these preparations could not be attributed to their content of vitamin A Grollman and Harrison (1943a, b) showed that fish oils and cod liver oil contained a substance capable of reducing blood pressure in hypertensive rats. The nature of the depressor substance is still unknown It appears to be a product of oxidation of some constituent (probably unsaturated fatty acids) present in various fish oils (Grollman, 1944) It is also possible that it is a quinone analogous to that which Friedman, Soloway, Marrus and Oppenheimer (1942) found to be effective in the treatment of hypertension The relation, if any, of this substance with the principles present in renal extracts is unknown

Moss and Wakerlin (1944) administered vitamin B (0 15 mgm thiamine, 0 01 mgm riboflavin, 0 15 mgm pyridoxine, 2 mgm nicotinic acid, and 0 4 mgm pantothenic acid) daily to one dog with renal hypertension without obtaining a fall of blood pressure. Neither ascorbic acid (1 gm daily) for four months nor 100 mgm. of vitamin E daily (equivalent to 60 mgm alpha-tocopherol) had depressor effects

ACTION OF RENAL EXTRACTS

In Chapter IX we discussed the fundamentals of renal organotherapy in the treatment of renal hypertension and mentioned the results obtained in hypertensive animals and man Here we will present some details of technique and complete the bibliography

Grollman, Harrison and Williams (1940c) were the first to demonstrate that it is possible to reduce the blood pressure of hypertensive rats to normal levels through the administration of renal extracts. After several trials, these authors adopted the following method of preparation of their extracts (Grollman, Harrison and Williams, 1942) Pig kidneys were dehydrated with alcohol and dried. The

resulting powder was extracted with acidulated water and then precipitated with 1 5 volumes of a saturated solution of ammonium sulphate The precipitate was dialyzed. The proteins and other inert materials remained within the sac while the active material passed through the membrane. The aqueous extract thus obtained was concentrated by making use of its relative insolubility in organic liquids (alcohol, acetone, ether), its adsorbability, and its ability to form insoluble compounds in the presence of certain precipitants The authors administered this extract by mouth.

Harrison, Grollman and Williams (1940) first studied the effect of renal extracts prepared by various methods and administered them to rats made hypertensive by subtotal nephrectomy. The intramuscular or intraperitoneal injection of such extracts produce toxic symptoms. They therefore resorted to oral administration which was found to be equally efficacious. The blood pressure fell soon after beginning the treatment and was maintained at a low level for several days In these cases the fall of pressure was accompanied by severe symptoms and at times death. It was not possible to decide whether these effects were due to impurities of the extracts or to the fall of blood pressure.

Williams, Grollman and Harrison (1940) then observed a fall of pressure in eight hypertensive dogs given the extract intravenously or intraperitoneally These animals also showed toxic symptoms in the majority of cases These authors therefore turned to the oral route of administration and treated ten dogs. Toxic symptoms, which the authors attributed in part to impurities of the extract and in part to the fall of the blood pressure, were often observed

Finally, Grollman, Williams and Harrison (1940b) administered their extracts to five hypertensive patients employing the oral or intravenous route They subsequently extended this study to eleven cases (Grollman, Williams and Harrison, 1942). They observed a more or less pronounced fall of pressure occasionally accompanied by diarrhea, nausea and vomiting which they believed to be attributable to impurities in the extract. In a recent article, Grollman, Williams and Harrison (1942) summarized their experience with the use of renal extracts in hypertensive rats, dogs and patients and stated that a fall of blood pressure and clinical improvement had followed the administration of renal extracts to a few hypertensive patients. They were unable to exclude the possibility that the improvement observed was spontaneous.

Independently of Grollman, Harrison and Williams, Page and his collaborators employed renal extracts for reducing the blood pressure of hypertensive dogs, rats and patients The basis on which these invertigators used renal extracts was the presumed existence of inhibitors to renin and angiotonin in animals tachyphylactic to renin and their disappearance in nephrectomized animals as well as the disappearance of the supposed activator of angiotonin in animals *injected with renal extracts It should be mentioned that* none of these findings have been confirmed Later, Page, Helmer, Kohlstaedt, Kempf, Corcoran and Taylor (1943) believed that the substance responsible for the fall of blood pressure observed was angiotonase contained in their extracts and endeavored to relate the destructive action on hypertensin *in vitro* with the depressor activity. Angiotonase is the same substance as hypertensinase which had previously been described and studied by Leloir, Muñoz, Braun-Menéndez and Fasciolo (1940a) and Fasciolo, Leloir, Muñoz and Braun-Menéndez (1940b)

After a number of trials these authors advocated the following method of preparation of the extracts (Page, Helmer, Kohlstaedt, Kempf, Corcoran and Taylor, 1943) (a) extraction of fresh pig kidneys with an aqueous solution of acetic acid and sodium chloride, (b) heating to 56°C in order to precipitate part of the inactive proteins; (c) precipitation of the filtrate with saturated ammonium sulphate; (d) redissolving the precipitate and adding ammonium sulphate to a concentration of 25 per cent saturation; (e) dialysis of the supernatant in order to eliminate the ammonium sulphate and then concentration *in vacuo* until 1 cc of the extract is equivalent to 100 to 170 gm. of kidney. (f) addition of an antiseptic and filtration by Seitz filter

Page, Helmer, Kohlstaedt, Fouts, Kempf and Corcoran (19[illegible]) described the results obtained with extracts of muscle, lung and [illegible] prepared by several methods The intramuscular or subcutaneous [illegible]

they obtained striking improvement in the eyegrounds and [illegible] and renal function

In later articles, Page, Helmer, Kohlstaedt, Fouts [illegible] (1941); Page, Helmer, Kohlstaedt, Kempf, Gambill [illegible] (1941); and Page, Helmer, Kohlstaedt, Kempf, Corcoran [illegible]

(1943) described the results of treatment with renal extracts in a large number of experimental animals and in a large number of patients with hypertension In all cases they obtained falls of pressure and in many improvement of clinical symptoms In the animals as well as in man, renal extracts produced a relaxation of the afferent arteriole of the glomerulus together with an increase of effective renal blood flow (Corcoran, Kohlstaedt and Page, 1941b), which they attributed to the presence of hypertensinase in their extracts The authors mentioned that in many of their patients the injection of the extracts produced local reactions (inflammation, pain) and general reactions (shock, fever) which perhaps had contributed in causing the blood pressure to fall although they did not believe that this was the principal cause.

Goldblatt, Kahn and Lewis (1942) injected renal extracts prepared by the method of Page, Helmer, Kohlstaedt, Fouts and Kempf (1941) into hypertensive dogs. In some dogs the pressure remained unchanged while three died as a result of the injection With extracts prepared according to the technique of Grollman, Williams and Harrison (1940a), the result was no better. In some dogs the subcutaneous injection of the extract produced a fall of pressure but it was almost always accompanied by a local reaction. In three rats the effect was nil As we shall see later, Goldblatt believed that the renal extracts acted nonspecifically.

Other authors have repeated the experiments of Grollman and collaborators and of Page and collaborators Jensen, Corwin, Tolksdorf, Casey and Bamman (1941) prepared a renal extract by a combination of the methods of Page and collaborators and of Grollman, Harrison and Williams, which when injected intramuscularly to rats made hypertensive by perinephritis or subtotal nephrectomy produced falls of pressure. Oral administration gave negative results Friedman, Jarman and Marrus (1942) obtained falls of pressure in rats made hypertensive by perinephritis by the subcutaneous injection of renal extracts prepared according to the method of Page and collaborators Rockwell (1942) described falls of pressure in five hypertensive patients who received daily intramuscular injections of a renal extract prepared by his own method. This extract was tried by Goldblatt, Kahn and Lewis (1942) in three hypertensive dogs without obtaining a fall of blood pressure Wakerlin, Goldberg and Moss (1944) treated two dogs with spontaneous hypertension

with renal extracts and obtained falls of blood pressure without apparent toxic side-effects Remington, Cartland, Drill and Swingle (1914) and Remington (1915) separated a protein fraction from hog kidneys by precipitation with ammonium sulphate and acetone. Extracts were also obtained from other tissues Depressor activity was found to be particularly potent in extracts of horse serum The authors described an assay method based on pressure reduction following four twice-daily injections into hypertensive rats and defined a unit of activity

Murphy, Grill, Langenfeld, Kurten and Guenther (1942) and Zithis, Wald, Thomas and Barker (1941) prepared renal extracts which were active in hypertensive patients Murphy and collaborators treated eleven patients with malignant hypertension, seven of whom responded satisfactorily to the treatment

There is no doubt that the treatment of human hypertension by renal extracts is still in the experimental phase Harrison, Grollman and Williams, and Page and his collaborators are in agreement with this statement They do not consider their own results convincing.

As regards Page who is more enthusiastic, he recognizes that the use of these extracts is not devoid of danger and because of unpredictable and occasional severe reactions, he advocates their use only within a hospital He does not believe that the reactions are the main cause of the fall of blood pressure

In the hands of Page and his collaborators, renal extracts produced a definite fall of blood pressure in patients with essential or malignant hypertension and an improvement of some symptoms and clinical signs were obtained Other authors have not observed this Schales, Stead and Warren (1942) obtained no success in seven patients treated by the intramuscular injection of renal extracts In those in whom a fall of blood pressure was obtained, local symptoms of inflammation or pain or generalized reactions were observed The injection of extracts with little hypertensinase produced falls equal to those obtained by extracts rich in hypertensinase

At the moment we are inclined to believe that the hypotensive effect obtained is not due to the specific action of some principle contained in renal extracts The introduction of foreign proteins into the body can produce general reactions of shock-like character accompanied by hypotension Effects similar to those resulting from

the administration of renal extracts are obtained with extracts of mushrooms, heated to destroy tyrosinase (Prinzmetal, Alles, Margoles, Kayland and Davis, 1942), products of digestion of casein (Prinzmetal, personal communication), pyrogenic inulin (Chasis, Goldring and Smith, 1942), milk, antityphoid vaccine (Scott, cited by Goldblatt, Kahn and Lewis, 1942), and so forth. Local inflammatory reactions can also produce falls of pressure in hypertensive individuals as we shall see later.

In regard to the hypotensive action of renal extracts administered by mouth as described by Harrison, Grollman and Williams, this has still not been confirmed. Jensen and collaborators (1941) mentioned negative results.

ACTION OF OTHER NONSPECIFIC AGENTS

It is well known that such diverse conditions as shock, abscesses, infectious diseases, malaria, and coronary thrombosis frequently produce a fall of blood pressure in hypertensive patients. In the dog, distemper causes a fall of pressure almost to normal levels as Levy and Blalock (1938), Katz, Friedman, Rodbard and Weinstein (1939), Wakerlin, Gaines and Mosny (1940), Goldblatt, Lewis and Kahn (1942) and ourselves have observed. Levy and Blalock, and Goldblatt and his collaborators report that distemper prevents the rise of blood pressure following constriction of the renal artery.

Rodbard, Katz and Sokolow (1940) claimed that the subcutaneous implantation of renal tissue caused the pressure of hypertensive dogs to become normal Goldblatt and Kahn (1941b), however, showed that if infection is avoided, the implantation of kidneys does not produce any effect. Friedman, Jarman, and Marrus (1942) observed the same in rats. When the rats developed an infection, the blood pressure fell whether the implanted tissue was kidney, liver or spleen. Rodbard and Katz (1943) have insisted, however, that the implantation of kidney has a greater depressor effect in hypertensive dogs than implants of other organs. Levy and Blalock (1938) and Goldblatt, Kahn and Lewis (1942) obtained falls of pressure in dogs by producing mixed infections with the formation of subcutaneous abscesses. In dogs thus infected, constriction of the renal arteries was incapable of producing hypertension.

Levy and Blalock (1938) were the first to indicate that fever produced by the intravenous injection of typhoid vaccine was ac-

companied by a fall of pressure in a hypertensive dog which was confirmed in a greater number of animals by Goldblatt, Kahn and Lewis (1942) and in man by Chasis, Goldring and Smith (1942). On the basis of these observations, some have applied this treatment to human hypertension, obtaining in some cases a fall of pressure and clinical improvement as Chasis, Goldring and Smith (1942) described Caution must be exercised, however, in the use of this therapy. The intravenous injection of typhoid vaccine can produce renal complications in patients whose kidneys are not perfectly normal (Taylor and Page, 1943a) Fever produced by exposing three hypertensive dogs to high environmental temperature also produces a fall in pressure (Levy and Blalock, 1938)

Immediately following the introduction of inulin for the measurement of glomerular filtration in man, it was observed that some samples of inulin were contaminated with pyrogenic substances (Goldring and Smith, 1936, Smith, Chasis and Ranges, 1938) This was probably of bacterial origin and produced, in addition to chills and fever, a marked renal hyperemia (Chasis, Ranges, Goldring and Smith, 1938, Smith, 1940, Smith, Chasis, Goldring and Ranges, 1940) It produced a fall of blood pressure especially in hypertensive subjects The previous administration of an antipyretic (amidopyrine) prevented the fever and the chills but not the renal hyperemia and the fall of pressure (Goldring, Chasis, Ranges and Smith, 1941) The intravenous administration of other pyrogenic substances such as glucose, distilled water, physiologic saline, typhoid vaccine, and tyrosinase also produced renal hyperemia and a fall of blood pressure It is the impression of Chasis, Goldring and Smith (1942) that the cause of this hypotension is attributable at least in part to an unfavorable reaction on the cardiovascular system more than to a correction of the fundamental disturbance causing hypertension. These authors have established the admirable criterion that whenever the blood pressure of hypertensive patients is lowered by the parenteral administration of a foreign protein, a pyrogenic reaction should be excluded before specific depressor properties are attributed to the substance used They caution against the administration of pyrogenic material because of the danger of inducing an alarming degree of peripheral circulatory failure In our judgment this statement summarizes admirably the present state of the problem of medical treatment of hypertension.

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TYROSINASE

Schroeder (1940, 1941) and Schroeder and Adams (1941a, b) thought that tyrosinase would constitute a rational therapeutic approach to hypertension on the theory that the renal pressor substance was a phenolic amine. Actually this enzyme has the property of oxidizing mono-dihydro oxyphenols and ortho-hydro oxyphenols to inactive quinones, the latter having no effect on blood pressure. Schroeder demonstrated that tyrosinase inactivated renin *in vitro* in the presence of catechol and also hypertensin This latter result has been confirmed by Croxatto and Croxatto (1941c, d) The injection of tyrosinase into hypertensive rats, dogs and patients produced a distinct fall of blood pressure and improvement of many of their symptoms The studies of Alles, Blohm and Saunders (1942) indicated that the amount injected by Schroeder and his collaborators was very much less than that which was capable of accelerating the oxidation of diphenolic amines

Furthermore, it is known that the injection of tyrosinase produces intense local reactions with or without fever which might well be the cause of the fall of pressure Prinzmetal, Alles, Margoles, Kayland and Davis (1942) obtained identical results in the treatment of hypertensive patients with an extract of mushrooms in which the *tyrosinase was inactivated* by heat

ANTIRENIN

Johnson and Wakerlin (1940a, b), Wakerlin and Johnson (1941a, b) and Johnson, Wakerlin and Goldberg (1941) attacked the problem of the neutralization of renin from the immunologic point of view Repeated injections into rabbits of an impure preparation of dog renin produced in the serum of these animals precipitants against the pseudoglobulins of the extracts and a principle called "antirenin" which neutralized *in vitro* the acute pressor action of the antigenic renin and also renin from other species. Antirenin was obtained in different animals by the injection of heterologous but not homologous renin.

We have not been able to obtain a neutralizing action of renin in the serum of dogs and rabbits which have been injected daily with pig renin for 30 to 40 days Perhaps our failure has been due to the fact that we have used preparations of renin which were more pure than those of Wakerlin and Johnson, and perhaps due to the fact that

we have not continued the injections over a sufficient length of time. Winternitz, Mylon and Katzenstein (1941b), and Friedman, Kruger and Kaplan (1942) were also unable to demonstrate the presence of antirenin in the serum of dogs injected with renin despite following the technique of Wakerlin and collaborators in all their details

Goldblatt, Katz, Lewis, Richardson, Guevara-Rojas and Gollan (1943) produced antirenin in the serum of dogs injected with renin intramuscularly In these animals the intravenous injection of renin even in large doses was incapable of producing a rise of pressure The serum of these animals also destroyed or inactivated renin *in vitro* as evidenced by the fact that the injection of a mixture of renin and its antiserum did not produce a pressor effect in normal dogs

The antiserum produced by injections of pig renin acts *in vivo* or *in vitro* against the renin of other animals but not against human renin (Goldblatt, Katz, Lewis, Richardson, Guevara-Rojas and Gollan, 1943, and Johnson, Smith, Gomberg and Wakerlin, 1943)

If renin were the pressor agent in hypertensive dogs, the repeated injection of heterologous renin would produce antirenin and thus would neutralize *in vivo* the pressor action of the animal's own renin. Wakerlin and his collaborators applied this form of treatment to dogs made hypertensive by renal ischemia and to dogs with spontaneous hypertension (Wakerlin, Johnson and Gomberg, 1941). Daily intramuscular injections of pig renin for four months produced a marked lowering of blood pressure in four dogs with renal hypertension while pig renin, inactivated by boiling, and dog renin were inefficacious The serum of dogs treated with pig renin neutralized the acute pressor action of renin

In the experiments of Wakerlin, Johnson and his collaborators, there are several weak points In the first place the extracts employed were very impure so that it is possible that the depressor effect was due to some impurity Wakerlin, Johnson, Smith, Moss and Weir (1943) were not sure that it was due to the renin itself since purer preparations of renin were less active Furthermore in one of the dogs treated with pig renin in which the antirenin titer of the serum remained essentially unaltered for twelve months after stopping the treatment, the blood pressure slowly rose until it reached the hypertensive level which was present before the treatment. It therefore can not be said that in this dog the reduction of blood pressure which followed injections of renin was due to the appearance of

antirenin in the blood Wakerlin, Johnson, Smith, Moss and Weir (1942) and Wakerlin, Johnson, Smith, Gomberg, Weir, Moss and Goldberg (1943) stated that their results could not be explained by the presence of antirenin Furthermore, neither Friedman, Kruger and Kaplan (1942) nor Williams (discussion of Wakerlin and Johnson, 1941b), nor Goldblatt, Kahn and Lewis (1942) have been able to repeat these results which Wakerlin and his collaborators had obtained in only a small number of animals.

Wakerlin, Johnson, Smith, Moss and Weir (1942), Wakerlin, Johnson, Smith, Gomberg, Weir, Moss and Goldberg (1943), and Wakerlin, Johnson, Kamm, Goldberg, Donaldson and Gomberg (1945) treated fifteen dogs with renin before attempting to produce hypertension by constriction of the renal artery. Pig renin was administered for two to three months to four dogs After producing renal ischemia, two of them developed hypertension and two did not. Four dogs received inactivated pig renin for one and a half to two months. Constriction of the renal artery produced hypertension in three and no change in pressure in one. Four dogs received dog renin for three months before constricting the renal arteries Two developed hypertension and two did not. In one dog which received rabbit renin three months before constriction of the renal artery, no hypertension developed Injections of inactivated human renin were not capable of preventing the blood pressure rise due to renal ischemia in two dogs In summary, of fifteen dogs submitted to a "prophylactic" treatment with different preparations of renin, six did not develop hypertension in contrast with sixteen untreated controls, all of which developed hypertension after renal ischemia. The authors concluded that the injections of renin had exercised a prophylactic action and had prevented the development of hypertension As regards the mechanism of action, the authors excluded the intervention of antirenin and doubted if the action could be attributed to renin or to other substances contained in the injected preparation Wakerlin, Johnson, Moss and Goldberg (1944) observed a depressor effect from renal extracts even after heat inactivation under which circumstances no antirenin appeared in the serum In a more recent publication, Johnson, Wakerlin and Smith (1941) reported that the immune substance was found in the pseudoglobulin fraction, was destroyed at 75 to 80°C for one half hour, and that it

followed the general behavior pattern of an antihormone Goldberg and Wakerlin (1944) were unable to obtain an "antihypertensin" in dogs given hypertensin from several sources intramuscularly for five months or injected with hog renin

Goldblatt (personal communication, 1945), has studied this problem and found that dogs vary greatly in their ability to produce antirenin when injected subcutaneously or intramuscularly with partially purified and highly purified sterile hog renin The development of a high antirenin titer in the blood produced by injecting partially purified sterile hog renin into dogs with experimental renal hypertension was accompanied by a gradual fall of the blood pressure to normal. In dogs with a high antirenin titer in the blood, constriction of the renal arteries was not followed by the development of hypertension No local, febrile, or other reactions were detected in the dogs so treated if the material injected was sterile

It is difficult to judge the significance of these studies on antirenin The preparations of renin injected by Wakerlin and his collaborators and by Goldblatt were not pure and, just as renal extracts can produce falls of pressure in hypertensive animals, these may have had the same effect through a similar action It is possible that the fall of blood pressure and prevention of hypertension were due to the injection of a foreign protein Since the injected renin was not pure, here is a further but rather remote possibility that an antibody gainst some other renal pressor substance was formed as well as the tibody to renin Goldblatt observed no manifestations of a foreign otein reaction despite careful search The evidence presented by n gives strong support to the thesis that renin is the substance responsible for the elevation of blood pressure in both acute and nic experimental renal hypertension

QUINONES

g and Zucker (1941a, b) showed that the injection of dienylalanine into ischemic kidneys produced an increase of pressure due to the formation of hydroxytyramine As a result observation, Bing formulated the hypothesis that the deamiof amino acids in the kidney is catalyzed by amine oxidases uires the presence of oxygen. Under anaerobic conditions night exist in renal ischemia, decarboxylation of amino acids

would occur without resulting deamination, thus giving rise to the formation of pressor amines, the accumulation of which would produce hypertension

Certain pressor amines may be inactivated by precursors of quinones (Oster, 1942) Friedman, Soloway, Marrus and Oppenheimer (1942) tested the action of a group of quinones on the blood pressure of normal and hypertensive rats Of ten quinones tested, four produced falls of blood pressure in hypertensive rats without affecting the pressure of normal rats. These four quinones were sodium rodizonate, an orthoquinone of little stability; trimethylparaquinone which produces toxic symptoms; and 2-5 dimethylparaquinone (xylo quinone) and 2 methyl, 5 isopropylparaquinone (thymoquinone) both of which when administered by injection or orally lowered blood pressure without producing hyperthermia or toxic symptoms

The mechanism of action has as yet not been elucidated According to the above authors, the quinones might act by destroying or inactivating pressor amines, by conjugation, by the formation of Schiff bases, or by acting as catalyzers of oxidative deamination

Oster and Sobotka (1943) tested several orthoquinonic derivatives of adrenalin on the blood pressure of normal and hypertensive rats The intramuscular or intraperitoneal injection of 2-iodo adrenochrome (10 to 100 mgm. daily for four to six days) and of 2-bromo adrenochrome in similar dosage produced a fall of blood pressure in hypertensive rats but not in normal rats The pressure fell to normal levels without the appearance of fever or toxic manifestations and returned to their initial level on suspending treatment.

Schwarz and Ziegler (1944) observed an antipressor effect in hypertensive rats of vitamin K which is a quinone As Grollman (1945) pointed out, the dose of 10 mgm employed suggests a nonspecific toxic effect In 1 mgm. dosage, Grollman found it to be ineffective in reducing blood pressure Oppenheimer, Soloway and Lowenstein (1944) reported the effects on blood pressure of several quinones and noted promising depressor effects in hypertensive rats and dogs following the administration of 1,4-cyclohexandione. Oppenheimer, Lowenstein and Hyman (1944) found that 1,4-cyclohexandione intramuscularly in a dosage of 10 mgm per kgm. lowered the blood pressure of hypertensive dogs and rats but had no effect on the blood pressure of normal dogs and rats No toxic symptoms were observed. A latent period of three to seven days intervened between the ad-

ministration of the drug and the fall of pressure After the injections were stopped, a somewhat longer interval elapsed before the blood pressure returned to its initial hypertensive level The mechanism of action is obscure Dexter and Haynes (personal communication) have observed that 1,4-cyclohexandione has no inhibiting effect on the reaction between renin and hypertensinogen, no destructive action on hypertensin, and causes no apparent reduction in the sensitivity of dogs to renin and hypertensin several days after the daily administration of 10 mgm per kgm intramuscularly

Advances in experimental hypertension of renal origin have raised hopes of obtaining a specific treatment for human hypertension

Of the large number of drugs employed either empirically or because of certain pharmacologic properties, none have shown particular promise in the treatment of hypertension Potassium sulfocyanate is useful in some cases and some marine oils appear to contain a substance with a prolonged depressor action

Different theories concerning the pathogenesis of essential hyper-ension have served as a basis for other attempts at specific therapy enal extracts and extracts rich in tyrosinase have produced falls of ood pressure and improvement of symptoms in hypertensive pa-nts, dogs and rats Existing evidence, however, suggests that this ect is due to a nonspecific action of foreign proteins

he treatment of hypertension in dogs by the injection of renin the purpose of producing antibodies to this substance is still g studied

nally, based on the theory that hypertension of renal origin is utable to the formation of pressor amines, the use of quinones ther substances has been attempted with success in dogs and he mechanism of action might be the neutralization of pre-pressor amines It is still not possible to draw definite con-s as to their specificity

CHAPTER XVII

SURGICAL TREATMENT OF HYPERTENSION OF RENAL ORIGIN

The lack of an effective medical treatment for hypertension, the rôle of the vegetative nervous system and of the kidneys in the production of experimental hypertension, and recent improvements in surgical technique have led to a search in the surgical field for a solution to this important medical problem In the last ten years a series of procedures have been developed Surgeons have attacked the problem by operating on (a) the kidney, (b) the adrenal glands, and (c) the sympathetic nervous system We will discuss the results obtained and consider especially their relation to the renal origin of hypertension

OPERATIONS ON THE KIDNEY

NEPHRECTOMY In Chapter XIII, it was mentioned that an appreciable number of cases of hypertension are associated with unilateral renal lesions (pyelonephritis, tumors, stones, lesions of the trunk of the renal artery, and so forth) Butler, in 1937, reported a case of hypertension due to unilateral pyelonephritis which was cured by *nephrectomy Since then, similar cases have been* published by a number of authors[1] Friedman, Selzer, Kreutzmann and Sampson (1942) studied renal blood flow before and after nephrectomy and

[1] Crabtree, 1927, Barker and Walters, 1938, Bradley and Pincoffs, 1938, Crabtree, 1938, Boyd and Lewis, 1938, Leadbetter and Burkland, 1938, Barney and Suby, 1939, Morton, 1939, Bothe, 1939, Mulholland, 1939, Oppenheimer, Klemperer and Moschkowitz, 1939, McIntyre, 1939, Braasch, Walters and *Hammer*, 1940a, b, Nesbit and Ratliff, 1940, 1941; Bartels and Leadbetter, 1940, Howard, 1940, Everett, 1940, Palmer, Chute, Crone and Castleman, 1940; Koons and Ruch, 1940, Patch, Rhea and Codnere, 1940, Barker and Walters, 1940a, Schroeder and Fish, *1940;* Barker and Walters, 1940b, c, Horton, 1940, Crabtree and Chaset, 1940, Lobo Onell and *Diaz Muñoz, 1941, Kennedy, Barker and Walters,* 1941; Abeshouse, 1941; Ratliff and Conger, 1942, Gibson, 1942, Friedman, Moschkowitz and *Marrus*, 1942, Farrell and Young, 1942, O'Conor, 1942, White, Durkee and Mirabile, 1943, McMartin and McCurdy, 1943, Weiss and Chasis, 1943, Sweeney and Pace, 1943, Semans, 1944, Kennedy, Barker and Walters, 1944, Dean and Abels, 1944.

observed a definite increase after operation, even in those patients in whom the blood pressure did not fall appreciably Weiss and Chasis (1943) observed the same in one case It is generally accepted that unilateral renal lesions usually are not accompanied by hypertension The statistics of Braasch, Walters and Hammer (1940a, b) and Shure (1942) demonstrate this clearly There are many cases in which the renal disorder is a coincidence in the course of hypertension This confronts the clinician with the problem of deciding in what cases the hypertension depends on the renal disorder and is amicable to nephrectomy, and in which cases it is coincidental. A number of factors must be evaluated

The first is the age of the patient When the patient is young, it is fairly probable that the hypertension is due to the unilateral renal lesions and benefit from nephrectomy may be anticipated if the hypertension has not lasted too long. When the age is over 40, the possibility of a simple coincidence of diseases is more likely Palmer, Chute, Crone and Castleman (1940) stated that nephrectomy was rarely beneficial for hypertension in women over 45 years or in men over 50 despite the presence of unilateral renal disease.

The second factor to be taken into account is the duration of the hypertension Although at first hypertension may be the result of a unilateral lesion, it eventually produces vascular lesions in the opposite normal kidney which in themselves are capable of maintaining the hypertension The experimental data of Wilson and Byrom (1941), Patton, Page and Ogden (1943) and Gaudino (unpublished) support this view It is not known how long hypertension can persist without producing lesions in the opposite kidney. Schroeder and Fish (1940) do not advise nephrectomy for high blood pressure if the hypertension has been present for more than two years

A third factor is the type of hypertension present Malignant hypertension contraindicates the operation since the necrotizing arteriolar lesions of this type of hypertension are located in both kidneys or only in the previously normal kidney (Leiter, 1938, Saphir and Ballinger, 1940; Schroeder and Fish, 1940)

A fourth factor is the character of the lesion which affects the kidney. Pyelonephritis is without doubt the most frequent unilateral lesion leading to hypertension. It is also the type in which nephrectomy has benefited the hypertension in the greatest number of cases In noninfected nephrolithiasis, hypertension is usually a coin-

cidence (Palmer, Chute, Crone and Castleman, 1940, Crabtree and Chaset, 1940; Braasch, Walters and Hammer, 1940a, b) The same is true of perinephritis and cortical abscesses.

Smith, Goldring and Chasis (1943) and Goldring and Chasis (1944) have recently pointed out that of 76 reported cases of hypertension associated with unilateral renal disease undergoing nephrectomy, the hypertension could be considered as cured in only seven Sensenbach (1944) reviewed the results obtained in 75 hypertensive patients nephrectomized for unilateral renal disease Using strict criteria, the author considered that the hypertension had been cured in five One-third of the cases had normal blood pressures but had been followed for less than two years, one-third had a fall of blood pressure but were still hypertensive, and in one-third the blood pressure was unchanged or higher This emphasizes the fact that considerable caution must be exercised in deciding upon nephrectomy with the hope of lowering blood pressure

In summary it may be said that in patients with unilateral renal disease, nephrectomy is indicated for hypertension in young patients, especially in those with atrophic pyelonephritis with uncomplicated benign hypertension which has been present for no more than two years. The number of cases actually cured by this procedure is exceedingly small, due presumably to vascular changes in the opposite kidney.

Before performing nephrectomy, renal function should be carefully investigated in each kidney separately. This should include studies of glomerular filtration with inulin, of excretory capacity with diodrast, and of renal blood flow with diodrast. It would also be of interest in these cases to study the ability of the normal kidney to increase blood flow under different experimental conditions since this might give information in regard to the vascular state of the opposite normal kidney

NEPHROTOMY. Nephrotomy has been suggested as a treatment for unilateral lesions accompanied by hypertension As has already been discussed, however, nephrotomy does not correct the renal disturbances responsible for the hypertension. Actually, this operation produces areas of renal sclerosis which may involve the intrarenal vessels producing ischemia and a resulting hypertension (Braasch, Walters and Hammer, 1940a, b; Abeshouse, 1941). For this

Cerqua and Samaan (1938, 1939) were the first to use this procedure for treating experimental renal hypertension. By renal decapsulation and covering the kidneys with omentum, falls of blood pressure were obtained in dogs with hypertension from constriction of the renal artery. Interference with this circulation led to the re-establishment of hypertension These results were confirmed and emphasized by Mansfield, Weeks, Steiner and Victor (1939), and Weeks, Steiner, Mansfield and Victor (1940) who obtained appreciable falls of blood pressure in dogs with bilateral renal ischemia by unilateral omentopexy or splenopexy observing, as Cerqua and Samaan (1938, 1939) had previously shown, that section of the vascular connections between the kidney and the omentum or spleen restored the hypertension McNider and Donnelly (1939) likewise observed that omentopexy produced a pronounced revascularization of the renal tubules. Goldberg, Rodbard and Katz (1940), however, were unable to obtain a fall of blood pressure by approximating kidneys and denuded muscle

Abrami, Iselin and Wallich, in 1939, made use of this therapeutic procedure in man Two cases, one with glomerulonephritis and the other with malignant nephrosclerosis, were treated by omentopexy with rather unsatisfactory results Almost simultaneously Bruger and Carter (1939, 1941) performed this procedure in eight patients, in six of whom improvement of symptoms was observed for six to eleven months In one of them, dying two and one-half months after operation, the authors demonstrated vascular communications between the kidney and the omentum DeTakats and Scupham (1940) reported four cases of malignant hypertension treated by decapsulation and application of omentum or muscle to an incision in the renal cortex. There was no significant reduction of blood pressure in any of the cases. Ritter (1941) performed this operation in a patient with mild hypertension whose blood pressure a year after operation was entirely normal Results obtained in man by this therapeutic procedure have not been identical with those observed in animals. Despite this a collateral circulation has been established between the kidney and the omentum in some cases (Bruger and Carter, 1939). Differences in the results obtained in man and animals may be explained by a consideration of the nature of the renal ischemia in the two species In dogs ischemia is produced by narrowing the main artery, the intrarenal branches being normal.

of the anterior cord roots between the sixth dorsal and second lumbar inclusive. In 1936, Adson, Craig and Brown reported the results obtained in 29 patients operated by this procedure and considered that they were good in 13, acceptable in 6, and failures in 8 Page and Heuer (1935) subsequently performed this operation in two stages, the first consisting of vertebral laminectomy, and the second of section of the anterior roots in 17 patients, observing a favorable response in 12 as evidenced by a fall of blood pressure, changes in the eyegrounds, and disappearance of symptoms Similar results were reported by Heuer (1936) More recently Hyndman, Wolkin and Paul (1940) reported favorable results with a slightly modified technique. These patients, however, followed over a longer period of time, did not outlive similar unoperated cases (Heuer, 1937, Heuer and Glenn, 1941) The improvement of symptoms was no greater than that obtained by other less drastic procedures and this operation has, therefore, been abandoned at the present time

BILATERAL SUPRADIAPHRAGMATIC SPLANCHNICECTOMY AND LOWER DORSAL SYMPATHETIC GANGLIONECTOMY OPERATION OF PEET Peet, in 1933 (see Peet, 1935), extended the older operations of Piere (1927) and Rossi (1928) b sectioning the splanchnics and sympathetic chains including th tenth, eleventh and twelfth dorsal ganglia This was done by means of bilateral thoracotomy and resection of the eleventh rib. Peet, Woods and Braden, in 1940, analyzed the results obtained in 350 consecutive cases operated by this procedure over a period of about seven years and concluded that this operation was of great value in the treatment of hypertension The figures presented by these authors showed a significant reduction of blood pressure in 51.4 per cent of the cases, the pressure returning to normal values in 11 7 per cent Improvement of symptoms was observed in 86 6 per cent, while in 69.4 per cent more or less pronounced changes in the eyegrounds were observed The authors believed that although the most favorable results were obtained in patients under 30 years of age, neither age nor eyeground changes such as edema, angiospasm and choked discs, contraindicated the operation. The operative mortality in the group of patients studied was 3 4 per cent On the basis of these results, the authors believed that no other medical or surgical therapeutic measure gave such good results in hypertensive patients

described an increase in the size and in the muscularis of the adrenal veins in hypertensive patients. These observations, however, have not been confirmed recently by Dempsey (1942).

With the idea that this gland played an important rôle in the production of this disease, DeCourcy, DeCourcy and Thuss (1934) and DeCourcy (1936) removed about two-thirds of the adrenal glands in patients with hypertension. Galata (1929) and Monier-Vinard and Desmarest (1930) have similarly treated some cases. The results reported by these authors were promising. Later, however, Adson and Allen (1936), Crile (1938) and Paliard and Martin (1939) repeated these procedures alone or accompanied by more or less wide resection of the sympathetic nervous system and concluded that removal of the adrenal glands did not benefit these patients

In our opinion, the relation of the adrenal gland to renal hypertension has still not been elucidated physiologically. Since clinical and anatomic data in patients are scanty, we do not believe that operation on these glands is justified

OPERATIONS ON THE SYMPATHETIC NERVOUS SYSTEM

Brüning (1923), Pende (1923) and Danielopolu (1923) suggested splanchnic resection in order to eradicate the supposed abdominal vasoconstriction and to inhibit the adrenals which they considered to be the main factors responsible for hypertension. The first operation was performed by Piere (1927, 1932) and Rossi (1928) and consisted of unilateral splanchnicectomy. Details of early surgical attempts may be found in the publication of Martin (1938).

The series of experiments performed by Prinzmetal and Wilson (1936), Pickering (1936b) and more recently by Stead and Kunkel (1940) (see Chapter XV) showed that hypertension is due to a generalized vasoconstriction of humoral origin. Surgical sympathectomy, however, has gradually developed into a more and more extensive operation.

SECTION OF THE ANTERIOR CORD ROOTS In 1925, Rowntree and Adson described a case of *malignant hypertension* treated by lumbar sympathectomy without significant changes of blood pressure. The hypotension and sympathetic paralysis obtained by spinal anesthesia induced Adson and Brown to introduce, in 1934, a new technique in the treatment of this disease which consisted of section

time up to two years, and observed that in 48 per cent of the cases there was no improvement or that it was only transient In 28 per cent the blood pressure was reduced appreciably and in 24 per cent a reduction to almost normal levels was obtained during the period of observation. These authors noted a marked improvement of symptoms in a large number of the patients which bore no definite relation to the change of pressure More recently (1940), the same authors analyzed results obtained in 224 hypertensive patients followed over periods varying between months and five years In 13 per cent the authors considered the results to be good, in 18 per cent acceptable, in 39 per cent temporary, and in 30 per cent poor. According to Adson and Allen (1937), the results of operation can be fairly well predicted by the use of several preoperative tests They considered that operative results would probably be poor if the patient's blood pressure did not fall to normal or nearly to normal during the following procedures (a) administration of 6 doses of 0 03 gm of sodium nitrite at intervals of 30 minutes, (b) administration of 0 20 gm of sodium amytal each hour for 3 consecutive hours, (c) intravenous injection of a solution of 5 per cent pentothal intermittently until the fall of blood pressure is established, (d) hourly determination of the blood pressure during rest and sleep for 24 consecutive hours

The authors of this operation believe that subdiaphragmatic sympathectomy is an advisable operation since in their hands it has given no mortality, a good number of patients are benefited, and results can be fairly well anticipated by the preoperative tests described

This operation has been used by other surgeons Heuer and Glenn (1941) observed only transitory improvement in blood pressure in 18 cases In 12 cases, Leonard and Oughterson (1941) reported excellent results in 1 and moderate in 4 In our group this technique has been employed by Introzzi with variable results and by Patiño-Meyer, Lepera, Pataro and Pataro (1942) in 1 case in which resection was unilateral with a transitory fall of blood pressure and improvement of symptoms

RESECTION OF LUMBODORSAL SYMPATHETICS TRANSDIAPHRAGMATIC SPLANCHNICECTOMY OPERATION OF SMITHWICK This operation, which at the beginning was a combination of the two previously described, was devised by Smith-

and that the results were not temporary but persisted for years

Woods and Peet (1941) subsequently compared the mortality statistics of patients treated surgically and medically. In similar groups of patients with considerable hypertension and angiospastic changes in the eyegrounds, there was a 33 per cent survival for five years in those treated surgically, while in the control group treated medically, the mortality was 99 per cent Using similar criteria in selecting hypertensive patients, however, Flaxman (1944) has recently reported a 31 per cent mortality in 244 cases of hypertension treated medically and followed over a period of five to ten years. These statistics tend to detract from the value of those of Woods and Peet.

In 1942, Woods reported results obtained by supradiaphragmatic splanchnicectomy and lower dorsal ganglionectomy in a large number of patients and claimed to have obtained a fall of pressure in more than half of the cases. In 37.5 per cent, the pressure became completely normal

This opinion is not shared, however, by other surgeons White and Smithwick (1941) reported poor results in over 90 per cent of 66 cases treated by this procedure. Recently Bartels, Poppen and Richards (1942) reported that in 13 operated patients, 8 died approximately 20 months later, 1 survived 4 1/2 years; and the 4 remaining continued to have blood pressures similar to those observed before operation. Unencouraging results have also been reported by Page and Heuer (1937), Davis and Barker (1938), Rytand and Holman (1941), Bordley, Galdston and Dandy (1943)

SUBDIAPHRAGMATIC SPLANCHNICECTOMY WITH RESECTION OF FIRST AND SECOND LUMBAR GANGLIA OPERATION OF CRAIG AND ADSON. This operation was employed for the first time in 1932 by Craig (see Craig and Brown, 1934) and was developed especially by Adson and his collaborators at the Mayo Clinic in 1935 The operation consists of a lumbar approach with resection of both splanchnics, the celiac ganglion, and the first and second lumbar ganglia At first a large part of the adrenal glands was removed, but this has been omitted because the results did not show it to be beneficial. The operation is performed in two stages, one for each side with an interval of about ten days between the two stages. Allen and Adson (1938) reported results obtained in 156 hypertensives treated by this technique followed over a period of

Patients were divided into three types according to the width of the pulse pressure in relation to the diastolic pressure. The best results were obtained in those with narrow pulse pressures (type 1) which were less than one-half the diastolic pressure and the poorest in those with wide pulse pressures (type 3) which were 20 mm. Hg or more above one-half the diastolic pressures The results which were obtained were independent of the degree of vascular change as determined by renal biopsy There was a high incidence of regression of eyeground changes, being most apparent in those with the more advanced alterations Of 99 patients with abnormal electrocardiograms preoperatively, 63 5 per cent showed slight to striking improvement following operation Included in the series were 11 patients with pyelonephritis and hypertension, all of whom responded well to the operation. This statistical study of Smithwick suggests that many patients with hypertension, especially those with narrow pulse pressures, have been benefited by extensive sympathectomy from the point of view of blood pressure, eyegrounds and electrocardiograms

Ayman and Goldshine (1943) published a detailed report of 14 cases subjected to extensive sympathectomy. This is perhaps the most convincing account to date that this operation is beneficial. There was striking fall of blood pressure in five, some improvement in three, no benefit in five, and one died as a result of the operation Ayman stated that with improvement of blood pressure, the heart might gradually decrease in size, the electrocardiogram return to normal, symptoms disappear, and incapacity be replaced by completely normal activity lasting at least as long as five years He also observed that angina pectoris might disappear and was of the opinion that no medical therapy had ever equaled the results obtained in five of his 13 cases In no case, however, did the blood pressure fall entirely to normal Gambill, Hines and Adson (1944a, b) studied the circulatory changes following extensive sympathectomy and found that the pulse became faster, pulse pressure decreased, cardiac output (Grollman method) increased slightly, basal metabolic rate decreased, and leg volume unexpectedly decreased They pointed out the value of abdominal binders, leg cuffs, and paredrinol sulfate in patients with severe post-operative postural hypotension

CELIAC GANGLIONECTOMY OPERATION OF CRILE

Based on anatomic studies which, according to the author, demon-

wick (1940). It consists of splanchnic resection together with removal of the four lower thoracic and first lumbar ganglia

Smithwick considers that this operation, which is more complete, offers a greater opportunity of cure. After this operation, the patients have a definite postural hypotension which according to the author is an index of the wide area of denervation.

In 34 patients followed for a period of four months to two years, Smithwick concluded that this procedure is better than the others and that the results *are usually satisfactory providing there is no* previous renal damage. Of 8 patients with renal damage treated by this procedure, 7 were not benefited by the operation.

Palmer and Smithwick (1941) found improvement in 60 per cent of their patients treated by this procedure. They considered that benefit was derived either (1) as a result of pooling of blood in the splanchnic region with a resultant reduction of venous return, cardiac output, and blood pressure, or (2) from an elimination of hyperactive sympathetic vasoconstriction. It is also possible that pressor responses to posture, cold, psychic stimuli or physiologic emergencies become altered Bartels, Poppen and Richards (1942) found that of 41 patients treated by this procedure, 3 died, 13 had a satisfactory fall of blood pressure, 11 only a slight fall, and 15 no change. Grimson (1942) believed that the Smithwick procedure was the operation of choice for hypertension.

Hinton (1944) performed this operation on 40 patients with essential hypertension and reported striking improvement in the retinae and in symptoms in some of the patients Smithwick (1944) has recently reported the results of this operation on 156 patients followed one to five years. The minimal operation extends from the tenth dorsal to the first lumbar ganglia inclusive and the maximal from the sixth dorsal to the third lumbar inclusive The operative mortality was 2 8 per cent. Bilateral complete resection of the first lumbar is followed by inability to ejaculate in males Results were judged *according to the magnitude of the effect on the* horizontal resting *diastolic blood pressure* level and were as follows:

Group	Cases		Effect on Blood Pressure
	Number	Per Cent	
1	64	41 0	Lowering of 30 mm Hg or more
2	32	20 5	Lowering of 20 to 29 mm Hg
3	28	17 9	Lowering of 10 to 19 mm. Hg
4	17	10 9	Lowering of 4 to 9 mm. Hg
5	15	9 7	No change or higher blood pressure

sure, (b) an improvement of symptoms with transient fall of blood pressure, (c) an improvement of symptoms without change of blood pressure, and (d) no improvement in symptomatology The improvement of symptoms observed in the majority of patients with or without change of blood pressure is difficult to explain It must be remembered, however, that a number of therapeutic measures are capable of altering the symptomatology in hypertension, and that suggestion, itself, is quite effective. A surgical procedure of this magnitude may be capable of modifying the symptoms of many patients through its psychic effect, rest, dietary regimen, and so forth. The results obtained by Albanese, Vedoya and González-Videla (1942) are suggestive in this respect These authors found that symptoms disappeared for 15 to 60 days after novocainization of one or both splanchnics Some unknown factor, however, can not be excluded

(2) Transitory falls of *blood pressure* are observed in the majority of patients following sympathectomy and may be explained in several ways Hypertensive individuals frequently have periods of transitory aggravation of their disorder characterized by further rises of blood pressure, accompanied at times by eyeground changes, spasms, hemorrhages, and cerebral manifestations which can be controlled by various therapeutic measures, especially bed rest It is probable that some of the patients who have had a transitory improvement following operation belong to this group Secondly, it is known that prolonged bed rest, diet, surgical shock, reabsorption of exudate, infection, tissue trauma and any surgical intervention of considerable magnitude produce a transitory fall of blood pressure Volini and Flaxman (1939) and Adamson and Dubo (1943) reported that changes in blood pressure observed after abdominal operations were similar to those observed in the majority of cases of sympathetic resection Rojas, Smithwick and White (1944), however, were unable to confirm these reports Nonspecific operations on 100 patients with hypertension produced an immediate fall of blood pressure in many but the fall was not pronounced and in the great majority of cases persisted for only a short time Lumbodorsal sympathectomy by Smithwick in 100 cases produced a reduction of blood pressure in a great majority of the patients which persisted for a considerable period of observation Most important of all was the fact that the blood pressure did not fall until after the second stage of the operation

Since the nervous system undoubtedly exerts an influence on blood

strate an increase in size of the periaortic plexuses and based on studies of comparative anatomy, Crile concluded that hypertension is due to an overactivity of the sympathetic nervous system Although this concept is doubtful for reasons already discussed, Crile advocated resection of the celiac ganglion and denervation of the aorta with or without denervation and partial resection of the left adrenal

In 1939, Crile reported results obtained by this procedure in 175 cases and reached the conclusion that this operation can be expected to produce a permanent fall of blood pressure in 17 per cent of cases and an appreciable improvement in 87 per cent. These results were confirmed and extended subsequently to a total of 535 operated cases Crile believed that if the operation was performed early, cure of the disease might be obtained If done later, the results varied according to the stage of the disease.

SUBTOTAL OR TOTAL PARAVERTEBRAL SYMPATHECTOMY. OPERATION OF GRIMSON. Allen and Adson suggested total sympathectomy for the treatment of hypertension Grimson, in 1941, described the technique which consists of transthoracic resection, and at times also abdominal resection of the sympathetic chains including the stellate ganglion, both thoracic chains, the celiac ganglion, and frequently the first and second lumbar ganglia

Grimson, Alving and Adams (1941) found that this operation was well tolerated, and was followed by hypotension and loss of sweating, but no change in digestive, respiratory or urinary function. Grimson (1942) recently reported results obtained in 18 severe hypertensive patients treated by this procedure. Three died as a result of the operation Observations on the remaining 15 over a period of 4 to 24 months led the author to believe that the progress of the disease was stopped or retarded in all The operative risk in the late stages of this disease is evidently great It is still too early to decide what usefulness the procedure of subtotal or total sympathectomy will have The results, however, have been sufficiently encouraging to continue the use of this treatment

An analysis of the results of sympathetic surgery for hypertension should include its effect on (1) symptoms, (2) blood pressure, (3) cerebral vascular accidents, (4) retinal vessels, (5) cardiac function, (6) renal function, and (7) the progression of the disease.

(1) From the foregoing discussion, it is apparent that there may be (a) an improvement of *symptoms* with permanent fall of blood pres-

rapid *progression* of the disease becomes slowed down although it still progresses From other reports, this may be surmised. No detailed information is as yet available on this most important point, nor is there any explanation as to why this should, if it actually does, occur.

From a practical point of view, it is difficult to explain why some patients with hypertension of long duration apparently become definitely improved while others under the same conditions show no change According to most authors, results are best when the patients are young and the disease mild, but this is not always the case since many apparently severe cases with eyeground changes and frank elevation of blood pressure have been benefited by the operation. How can these apparent discrepancies be explained? How can the variable results obtained by the same procedure by different surgeons with recognized technical skill be explained? It is possible that these points which are still obscure may become clarified by a methodical study of the patients and of the character of their hypertension, and by meticulous follow-up studies It is to be hoped that more information will be forthcoming in the near future on the various points mentioned above.

Published statistics suggest that these operations have real importance. Because of the lack of benefit in experimental hypertension, the inconsistencies in published reports, and the relatively short period of postoperative observation, we believe that final judgment should be reserved at this time In our opinion, sympathectomy can not be considered as a cure for hypertension From what can be gleaned from the literature, however, it does appear to occupy a real place in therapy.

Of the numerous surgical procedures proposed for the treatment of hypertension, three are of value (a) nephrectomy, (b) nephropexy, and (c) sympathectomy Nephrostomy, renal denervation, omentopexy and adrenalectomy lack therapeutic value.

Nephrectomy may be indicated in cases with unilateral lesions preferably when the hypertension occurs in young individuals and when it is of short duration and without apparent vascular lesions It is important before deciding on nephrectomy to study renal blood flow in both kidneys separately and the functional capacity of both kidneys Diminution of blood flow and of function in the diseased

pressure in hypertensive individuals as manifest by rapid changes of blood pressure in response to a variety of emotional, painful and other stimuli, it would appear that extensive sympathectomy removes the majority of efferent pathways over which these impulses travel. It is presumably by this mechanism that blood pressure is lowered. In most patients, the blood pressure does not become entirely normal and in them the hypertension which does remain is obviously determined by some factor or factors other than the sympathetic nervous system.

(3) Little is known concerning the occurrence of *cerebral vascular accidents* following sympathectomy, except that such complications are a frequent cause of death. It would appear, although statistical analyses are not available, that this operation does not markedly affect their occurrence.

(4) *Retinal vascular changes* revert toward normal in many patients following sympathectomy. The significance of such improvement in relation to the general arteriolar system is not entirely clear.

(5) From the report of Ayman and Goldshine (1943), it is apparent that *cardiac function* may be improved to a variable degree, and at times dramatically, by extensive sympathectomy. The electrocardiogram shows changes in the direction of normal following operation in the majority of cases (Smithwick, 1944). It therefore appears that cardiac function is improved in a certain proportion of cases but a detailed analysis of this point has not as yet appeared

(6) Since renal ischemia is apparently a common cause of hypertension, it has been thought that the improvement observed in these patients might be explained by an increase of *renal blood flow* as a result of sympathectomy. Selzer and Friedman (1941), Corcoran and Page (1941c), Goldring, Chasis, Ranges and Smith (1941), Foà Woods, Peet and Foà (1942a, b, 1943), however, in extensive studies performed with inulin and diodrast have shown that renal blood flow is unaltered after sympathectomy. Recently Corcoran and Page (1941a) concluded that a diminution of pulse pressure was concerned with the liberation of renin by the kidney, and Foà, Woods, Peet and Foà (1943) considered that the favorable results observed in some operated patients could be attributed to this phenomenon. We do not believe, however, that this interpretation is entirely acceptable (see Chapter VIII)

(7) Grimson (1942) stated that following sympathetic surgery, the

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kidney without appreciable change in the normal kidney are important factors for deciding to operate. The existence of a moderate diminution of blood flow in the normal kidney is not a contraindication for nephrectomy since this possibly may be due simply to a functional alteration produced by pressor substances liberated by the diseased kidney.

Nephropexy may be indicated in isolated cases of orthostatic hypertension in which the existence of a diminution of renal blood flow in the upright position is demonstrated.

Sympathectomy Numerous operations on the sympathetic nervous system have been employed for this form of treatment of hypertension These include section of the anterior cord roots, bilateral supradiaphragmatic splanchnicectomy and lower dorsal ganglionectomy, subdiaphragmatic splanchnicectomy with resection of the first and second lumbar ganglia, celiac ganglionectomy, subtotal or total paravertebral sympathectomy, and lumbodorsal resection with transdiaphragmatic splanchnicectomy.

This latter, known as the operation of Smithwick, has apparently given the best results to date.

The operation gives best results in young subjects with a labile hypertension without vascular complications Certain tests have been devised for the preoperative selection of patients

The results obtained by different authors who have performed sympathectomy in a large number of patients are not in agreement.

In our judgment hypertension of long duration has little probability of being cured by sympathectomy. Sympathectomy, however, according to the existing data in the literature, is a therapeutic measure worthy of consideration for many cases of hypertension.

CHAPTER XVIII

HUMAN HYPERTENSION AND EXPERIMENTAL HYPERTENSION

In this chapter the relation between human and experimental hypertension will be discussed in order to point out similarities and differences existing between them and to formulate problems which are still unsolved and which may serve as a basis for further investigation References will be omitted in order to facilitate the discussion The reader will be able to find the original references in previous chapters

HUMAN AND EXPERIMENTAL RENAL HYPERTENSION

In Chapter XIII it was pointed out that all types of experimentally produced renal hypertension have their counterpart in human pathology Isolated cases have demonstrated in a more or less convincing manner that destructive processes of the parenchyma such as perinephritis, vascular lesions, and changes in the urinary tract are associated with hypertension, presumably in the same manner as in the experimental animal Histological evidence indicates that in man the presence and degree of hypertension parallel closely the existence and degree of renal vascular lesions When the renal process affects the vessels of both kidneys extensively as in glomerulonephritis and pyelonephritis, hypertension is almost constant In disorders of the urinary tract both in man and in animals, hypertension is almost always absent In bilateral lesions of the urinary tract, the frequency of hypertension in man is somewhat less than that observed after experimental obstruction of both ureters in the dog. These differences are logical because in man as a general rule disorders of the urinary tract affect renal function and circulation only slightly.

In the hypertension produced by unilateral renal lesions, removal of the affected kidney abolishes the hypertension in animals and occasionally in man. Recently Smith, Goldring and Chasis (1943) in a critical study of data in the literature, concluded that of 76 hypertensive individuals with unilateral renal lesions, only in 7 did

nephrectomy produce a definite and maintained fall of blood pressure. If it is assumed that the hypertension in these patients was due to unilateral renal ischemia, these results are different from what occurs in dogs since in this animal removal of the ischemic kidney is accompanied in all cases by a fall of blood pressure to normal levels These differences may be explained in two ways: (1) the differences possibly depend on the cause of the renal ischemia in man and in dog, on the time during which the hypertension has been maintained, or on the character of the renal lesion, (2) it is possible that man behaves like rats in respect to unilateral renal lesions *associated with hypertension. In these animals nephrectomy* becomes progressively less effective in curing hypertension produced by unilateral cellophane nephritis the longer the duration of the hypertension. This is due to the fact that the unilateral disorder rapidly leads to the appearance of irreversible lesions in the kidney on the opposite side Despite the similarity of the behavior of human and experimental renal hypertension, it must not be forgotten that in man the renal lesions may often be a simple coincidence This point deserves further study. Human hypertension of renal origin has the same characteristics as hypertension produced in animals by renal ischemia.

ESSENTIAL HYPERTENSION AND EXPERIMENTAL HYPERTENSION FROM RENAL ISCHEMIA

Studies of the characteristics of animals made hypertensive by constriction of the renal artery and of hypertensive patients have shown many similarities Lewis and Goldblatt (1942) have listed these in a *table which we have reproduced in a slightly modified* form (see Table 6)

It will be noted that there is a close similarity between essential hypertension in man and experimental renal hypertension in the dog while there are many differences between human essential hypertension and experimental neurogenic hypertension in animals.

In Chapter XIV, we presented anatomic evidence indicating that renal vascular lesions are demonstrable in most patients with essential hypertension In the majority of patients with essential hypertension, there is a certain degree of renal ischemia as indicated by *studies of* renal function. Both the anatomic and functional changes have been interpreted by some as indicative of a renal ischemic origin of

essential hypertension while others have considered them to be the result of the hypertensive process We have discussed the evidence from both points of view. We believe that the evidence points to the kidney as playing an important rôle in the production of essential hypertension

In the present state of our knowledge, we are unable to determine whether the renal changes which lead to hypertension are primary or whether in their production other mechanisms are involved. It is probable that the pathogenesis of this disease is somewhat similar to that of diabetes, as Smith, Goldring and Chasis (1943) have suggested Diabetes depends on changes in the pancreas which are primary or secondary to changes in other glands (hypophysis, adrenal, thyroid, and so forth) As regards hypertension, however, we believe that the mechanism by which blood pressure rises involves an anatomic or functional change in the kidney leading to its ischemia.

TABLE VI

Aspect Considered	Human Essential Hypertension	Experimental Renal Hypertension	Experimental Neurogenic Hypertension
Heart rate	Normal	Normal	Increased
Cardiac output	Normal	Normal	Increased
Blood volume	Normal	Normal	Increased
Blood viscosity	Normal	Normal	
Peripheral blood flow	Normal*	Normal	Increased
Sympathectomy	Often improves	Neither prevents nor cures	Prevents or abolishes almost completely
Splanchnicectomy	Often improves	Neither prevents nor cures	Prevents or abolishes almost completely
Renal blood flow	Reduced	Reduced†	Normal
Renal ex[illegible] functi[illegible]	[illegible]	[illegible]	[illegible]
Cardiac [illegible]	[illegible]	[illegible]	[illegible]ntricle—marked [illegible]t, dog
Pulmonary artery pressure	Normal, increased in left ventricular failure	Normal	[illegible]
Thyroidectomy	Neither prevents nor cures	Neither prevents nor cures	[illegible]
Retinal vascular changes	In late stages	In late stages	None‡
Generalized arteriolar necrosis and necrotizing arteriolitis	In malignant stage	In malignant stage	None

* Disputed Abramson and Fierst, 1942.
† Disputed Corcoran and Page, 1941b
‡ Dr Stanley J G Nowak: personal communication, 1945.

THE CHEMICAL MEDIATOR OF HYPERTENSION

As we have had occasion to point out in the course of this book, *it has been demonstrated that* renal ischemia liberates renin into the renal venous blood. The properties of renin depend on its capacity to form hypertensin when it is incubated with plasma or serum under appropriate conditions. Although renal ischemia under certain conditions is capable of liberating renin, and although this substance is found in the blood in certain types of renal hypertension, it does not necessarily follow that renin plays an exclusive rôle as the chemical mediator of hypertension. In order to consider that a substance is the cause of hypertension, it is necessary (1) that the physiologic effects produced by its injection reproduce the changes found *in hypertension, (2) that it be demonstrable in the blood of patients* with hypertension, and (3) that it be found in lesser amounts in the blood of patients with normal blood pressure.

Let us consider how renin satisfies these conditions.

(1) PHYSIOLOGIC EFFECTS OF RENIN: The pharmacologic effects of renin and the circulatory dynamics in hypertensive animals are summarized in Table 7, which is a modification of *that published* by Lewis and Goldblatt (1942) Analysis of this table reveals a good parallelism between the two Such similarities do not constitute a *proof but are compatible with the hypothesis that* renin is the chemical mediator of hypertension. Some other pressor substances which have been considered as causes of renal hypertension have pharmacologic characteristics which are dissimilar and make their participation unlikely Thus, for example, the pressor action of *adrenalin,* tyramine, guanidine and pitressin is accompanied by a strong constriction of skin vessels which is contrary to that observed in *hypertension and* in animals following an injection of renin. The injection of Fourneau 933 produces the same change in blood pressure in normal as in hypertensive animals, whereas it inverts the action of adrenalin This is evidence against the theory that adrenalin is concerned in hypertension Since cocaine is not capable of *abolishing* hypertension, it is most unlikely that tyramine is the causal agent Strong evidence that renin is the causal agent of chronic renal hyper*tension in animals* is the prevention and cure of experimental renal hypertension in dogs following the production of an elevated titer

TABLE VII

Aspect Considered	Effect of Intravenous Injection of Renin Into Normal Animals	Experimental Renal Hypertension
Heart rate	No change	No change
Cardiac output	No change	No change
Total sympathectomy	Pressor action not reduced	Blood pressure not reduced
Destruction of cord	Pressor action not reduced	Hypertension not abolished
Hypophysectomy	Pressor action not reduced	Dampened but not completely prevented or cured
Thyroidectomy	Pressor action not reduced	Neither prevented nor cured
Gonadectomy	Pressor action not reduced	Neither prevented nor cured
Acute adrenalectomy	Pressor action not reduced	Rise of blood pressure produced by ischemic kidney grafts not prevented
Chronic adrenalectomy	Pressor action reduced or abolished	Hypertension prevented or abolished
	Pressor action restored by desoxycorticosterone	Hypertension partially restored by desoxycorticosterone
Bilateral nephrectomy	Greater pressor effect	Greater rise of blood pressure produced by ischemic kidney grafts
Peripheral blood flow	Not reduced during rise of pressure	Not reduced in hypertensive rabbits
Renal circulation	Efferent glomerular arteriole constricted	Efferent glomerular arteriole constricted
Blood pressure		
a Fourneau 933	Pressor effect not inverted by Fourneau 933	F 933 produces same fall of blood pressure in normals and hypertensives
b Cocaine	Pressor effect not modified by cocaine	Cocaine produces no fall of blood pressure in dogs with hypertension from ligation of renal arteries
c. Pulmonary artery pressure	No rise of pressure in pulmonary artery	Pulmonary artery pressure normal
d. Duration of pressor action	Persistence of pressor action after a single injection no greater than 2 hours	Persistence of hypertension after removal of ischemic kidney usually greater than 6 hours
e Tachyphylaxis	Repeated injections produce tachyphylaxis	Persistent hypertension Normal or increased sensitivity to renin
f Permanent hypertension	Permanent hypertension has not been obtained by continuous injections of renin	Permanent hypertension

in the blood of antirenin by the intramuscular injection of heterologous renin The possibility that the blood pressure falls are due to the injection of foreign proteins can not, however, be entirely excluded even though no local or systemic reactions have been observed.

A most important point which has not been adequately studied is the possibility of producing persistent hypertension by continuous injections of renin If this could be done, it would not only reproduce the disease but would also demonstrate that tachyphylaxis is not

capable of preventing the development of hypertension. With adrenalin and with tyramine it has not been possible to obtain persistent hypertension.

It has been stated that since hypertensive animals are as sensitive or even more sensitive to the pressor action of renin than normal animals, renin can not be the etiologic agent responsible for hypertension. This is a plausible argument since the further addition of a substance capable of producing tachyphylaxis ought to produce a diminished response. The cause of renin tachyphylaxis is largely due to the reduction of hypertensinogen concentration in the plasma The presence of a normal hypertensinogen concentration in hypertension may possibly explain the normal sensitivity of hypertensive animals to renin.

A further argument against the rôle played by renin in the genesis of hypertension is that removal of the ischemic kidney in hypertensive dogs causes the blood pressure to return to normal in the course of about six hours or less while the falls obtained after injections of renin appear to be much more rapid It must not be forgotten, however, that injection experiments have been carried out with heterologous renin and that the dosage employed may have altered these responses.

Despite these objections, renin may still be the chemical mediator of hypertension. Some of these phenomena may be due to the presence of impurities which modify its action, although it is possible that hypertension is the result of the action of several pressor substances

(2) DEMONSTRATION OF RENIN IN THE BLOOD OF HYPERTENSIVE ANIMALS AND HUMAN BEINGS. Renin has been demonstrated in the renal venous blood and in the systemic blood of animals with renal hypertension during the acute phase of hypertension It has been demonstrated during the first days following ischemia, especially when the constriction of the artery is extreme and when accompanied by signs of severe renal insufficiency It has been detected in a few human beings during the acute phase of hypertension (acute glomerulonephritis, toxemia of pregnancy). In animals with chronic hypertension with or without renal insufficiency as well as in patients with essential hypertension, the most reliable results have been uniformly negative up to this time.

This difference between acute and chronic hypertension is a curious one and remains quite unexplained It is possible that the appearance of renin in the blood during the acute period of ischemia is due to autolysis of renal tissue as a result of the severe ischemia. In this case renin instead of causing the hypertension, would be the result of a destructive process. Another interpretation might be that renin is the initiator of a series of processes which lead to hypertension, which once produced persists providing the condition created by the renal ischemia persists. A third possibility is that due to the extreme ischemia during the acute phase, renin is produced in such large amounts that it can be detected by existing methods in the blood As the process becomes chronic, it diminishes in amount so that it is not recoverable by these methods but nonetheless capable of maintaining the hypertension Although there are many other possibilities for explaining these differences, it is useless to review them New investigations should be fruitful

From what has been said, we may conclude that renin does not fulfill satisfactorily the second condition It is to be hoped that with improvement of methods for the detection of renin this important point will be clarified

(3) DEMONSTRATION OF RENIN IN THE BLOOD OF NORMAL SUBJECTS. Renin has not been found in the blood of animals or human beings with normal blood pressure It has been possible, however, to detect it in the blood of patients and animals in a severe state of shock. This is in no way contradictory since under conditions of arterial hypotension, there is renal ischemia and, therefore, a liberation of renin The fact that the liberated renin is not capable of elevating the pressure is easily explained by the action of the various factors responsible for the shock.

From what has been said, there are a group of similarities between hypertension from renal ischemia and human hypertension. Although it can not be definitely stated that the two are identical, evidence indicates that in human hypertension the kidney plays an important rôle.

The crucial proof of the identity of both would be the demonstration in the blood of the renal pressor substance responsible for the hypertension. This proof is still lacking but it is to be hoped that new investigations will offer a solution to this important problem.

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APPENDIX

METHOD OF GRAFTING KIDNEYS BY VASCULAR ANASTOMOSIS

Dogs weighing 8 to 10 kgm. are anesthetized by injecting intravenously 10 cc of a warm 8 per cent solution of chloralose per kilo of body weight Both kidneys are removed through a midline abdominal incision. The femoral artery is prepared by the usual technique, and a glass cannula, connected with a recording manometer, is introduced The neck vessels are then dissected to make ready for the graft The jugular vein is exposed through an incision in the neck It is carefully separated from the surrounding tissues and cleared from the point where it enters the thorax to the level at which it divides into several branches high in the neck At this point, it is ligated and divided.

The plane between the neck muscles and the trachea is separated and the carotid artery is isolated from its accompanying veins and nerves The thyroid vessels must be ligated at its upper portion. At the level of the carotid sinus, it is ligated and divided.

Payr's cannulas, which facilitate the making of anastomoses, are now introduced into the carotid artery and the jugular vein We have used bronze cannulas of different sizes, the larger ones being reserved for veins and the smaller ones for arteries The vessel is passed through the lumen of the cannula with the help of small forceps The vessel is then turned back over the cannula and tied in such a manner that the endothelial surface is exposed within the lumen (see figure 23, page 82). The animal is placed on an operating table One or 2 hours are allowed to elapse before performing the graft in order to allow the operative shock to subside. A heated plate at 37°C is placed beside the animal in order to keep the temperature of the grafted kidney at 37°C.

The kidney of the donor animal is now removed. The dog is anesthetized with ether The abdomen is opened widely through a midline abdominal incision. The aorta and vena cava are rapidly dissected free at the level of the renal vessels. The kidney is freed by placing a ligature around the tissue at each pole of the kidney.

The aorta and inferior vena cava are cut above and below the origin of the renal artery and vein respectively. The ureter is cut and the kidney is removed from the abdomen. This procedure should be completed in 2 or 3 minutes.

The kidney is placed on the heated plate. The aorta and vena cava are opened longitudinally in order to locate the orifices of the renal vessels. The mouth of the renal vein is frequently hidden by a valve-like fold which may have to be divided. The Payr's cannula enclosed in the carotid vessels is now introduced into the renal artery through its aortic orifice. A ligature is placed around it in such a manner that there is a continuous layer of endothelium on the luminal surface. In the same manner, the jugular cannula is introduced into the orifice of the renal vein in the vena cava. These procedures are carried out without difficulty when normal kidneys are used. Using kidneys with the artery constricted by a Goldblatt clamp, however, difficulties are frequently encountered due to the fact that the renal artery has lost its elasticity and is extremely fragile. When the graft is successful there is a good circulation and an abundant secretion of urine.

PREPARATION OF RENIN

The cortex of 3 kgm. of pig kidneys is separated and ground to a pulp in a meat grinder. Three volumes of 6 per cent sodium chloride and 500 cc. of toluol are added. After stirring, the solution is left overnight at room temperature. The fats are skimmed off and the solid part is removed by squeezing through coarse cloth. The solution is acidified with acetic acid to pH 4 (green to bromcresol green). It is then centrifuged. The supernatant is filtered by suction through a Buchner filter using Celite Hiflo Supercell (Johns Manville Company).[1] Three hundred and ninety gm. of ammonium sulphate are added for each liter of filtrate. After dissolving, it is filtered as in the previous step. The precipitate is suspended in 1 liter of water and neutralized with sodium hydroxide. It is left overnight in the icebox in order to allow the renin to go into solution completely. It is then filtered. To the filtrate are added 250 gm. of sodium chloride per liter. Since this dissolves with difficulty, vigorous stirring is necessary. After several hours the solution is cooled. If crystals of salt appear,

[1] No more than an hour should elapse at this stage before adding ammonium sulphate.

they are separated by filtering through muslin. The pH is lowered to between 2 and 3 by the addition of 5 N hydrochloric acid It is then filtered. The precipitate is suspended in 500 cc. of cold water and as it is becoming redissolved, it is immediately neutralized. It is then filtered and the filtrate brought to a volume of 600 cc. This solution is maroon in color and is the one which has been used in our laboratory for the majority of experiments. It contains only traces of hypertensinase This hypertensinase can be completely destroyed by raising the pH to 9 or 10 for 15 to 20 minutes at room temperature.

PREPARATION OF SERUM GLOBULINS (HYPERTENSINOGEN)

Beef blood is collected in the slaughter house. The addition of an anticoagulant has been shown to be unnecessary since the fibrin separates spontaneously. The blood is centrifuged in a milk separator of the Laval or Sharples variety To each liter of serum, 300 gm. of ammonium sulphate are added Once dissolved it is left overnight in the icebox. It is then filtered for the next 48 hours through fluted paper in the icebox The precipitate is dissolved in warm water using one-quarter of the volume of the original serum and is neutralized with sodium hydroxide This solution can be used for the preparation of hypertensin. When used for other purposes, it is necessary to dialyze it due to the quantity of ammonium sulphate present.

PREPARATION OF HYPERTENSIN

Four liters of serum globulins, prepared as described above, are heated to 37°C and the amount of renin necessary for obtaining the complete transformation of hypertensinogen to hypertensin is added. This amount is determined by small scale experiments. In general, 1 liter of renin is used to obtain 1,000 units of hypertensin. After 15 minutes of incubating at 37°C., 15 liters of 96 per cent alcohol are added and the solution filtered The proteins may also be removed by pouring the mixture into 2 volumes of boiling water, then lowering the pH to 4 or 5, and filtering. Alcohol gives the purer preparation.

The filtrate is evaporated under reduced pressure to approximately 200 cc. It is placed in a separatory funnel and saturated with powdered ammonium sulphate and extracted three times with 5 to 10 cc of phenol The phenolic extract is filtered and to the filtrate are

added 10 cc. of water and 150 cc. of ether After shaking, the aqueous phase is separated and saved It is extracted twice more with 5 to 10 cc of water. The combined aqueous extracts are acidified and extracted several times with ether The ether is then evaporated from the aqueous extract by heating over a hot water bath It is made acid to Congo red with hydrochloric acid and heated for several minutes. It is then left for several hours in the icebox and filtered

PURIFICATION. The preparations thus obtained are very impure. Some of the impurities may be eliminated by resorting to one or more of the following procedures which can be repeated or combined in several ways

(a) *Precipitation by alcohol* The solution of hypertensin is evaporated to a small volume, and 4 volumes of 96 per cent alcohol are added Salts and other substances remain in the inactive precipitate

(b) *Precipitation by ether from ammoniacal alcohol* The solution of hypertensin is evaporated to dryness and the residue is extracted with 95 per cent alcohol containing 1 per cent concentrated ammonia It is then filtered Ether is added to the filtrate until precipitation of hypertensin is complete.

(c) *Precipitation by ether from acetic acid* The solution of hypertensin is evaporated to dryness and is extracted with glacial acetic acid It is filtered Ether is added to the filtrate until precipitation of hypertensin is complete

(d) *Extraction with phenol.* The solution of hypertensin is saturated with ammonium sulphate and is then extracted with phenol The hypertensin passes into the phenol, from which it may be extracted by water made slightly acid by hydrochloric acid This is accomplished by adding 10 volumes of ether and extracting several times with small amounts of water. The phenol passes into the ether and the hypertensin into the water

(e) *Adsorption and elution.* The solution of hypertensin is precipitated with 10 volumes of ammoniacal alcohol (0 1 N) The inactive precipitate is removed by filtration The hypertensin is adsorbed in a column of aluminum oxide prepared according to Brockman. It is eluted with 30 per cent alcohol This method has given us our purest preparation which contains 0 1 mgm. of nitrogen per unit.

Regardless of the method used, there is at times a tremendous loss of active substance.

ASSAY OF HYPERTENSIN

PRINCIPLE OF THE METHOD. The rise of blood pressure of an anesthetized dog produced by the intravenous injection of a solution of hypertensin of unknown strength is compared with the rise of pressure obtained with a standard solution of hypertensin of known potency.

TECHNIQUE. Due to their greater sensitivity, small dogs weighing 4 to 6 kgm are preferably used. Chloralose was previously used as the anesthetic. At the present time, nembutal or amytal (0 04 to 0 08 gm of amytal per kgm, 0.04 gm. of nembutal per kgm) are given by *mouth or by intraperitoneal injection. The animals must be fasting.* Pithing under ether anesthesia followed by artificial respiration sometimes provides satisfactory preparations. Once the dog is anesthetized the arterial and venous cannulas and the tracheal cannula are introduced by the usual technique Artificial respiration must be so adjusted that it is sufficient but not excessive It is advisable to maintain the pulmonary ventilation at the minimum *necessary to preserve the normal color of the mucous membranes* and yet sufficient to suppress spontaneous respiration of the animal Cooling of the dog may be prevented by using a heated table. The blood pressure is recorded on a kymograph by the use of a suitable recording manometer.

CRITERIA OF A GOOD PREPARATION. (a) *Sensitivity*—Sensitivity refers to the rise of pressure produced by a dose of hypertensin of known potency It varies from one animal to the next Generally speaking, 1 unit of standard hypertensin gives a rise varying between 20 and 60 mm Hg The greatest accuracy may be obtained when the animal is most sensitive *If 1 unit of hypertensin produces* a rise of less than 20 mm. Hg, it is better not to use the animal.

(b) *Constancy*—Since the sensitivity of the dog may vary from one moment to the next, the sensitivity must be checked repeatedly. A good preparation undergoes little change in sensitivity.

(c) *Regularity*—A good preparation shows no changes in heart rate, blood pressure or variations of blood pressure from respiratory causes.

It is relatively easy to fulfill the conditions of constancy and regularity, especially if pithed preparations are used As regards the

[illegible] of [illegible] we [illegible] [illegible] small animals.

Procedure.—The sample to be assayed is injected into the [illegible] vein. [illegible] [illegible]

The [illegible] of the blood pressure [illegible] is [illegible]. [illegible] of hypertensin is then injected in order to determine the sensitivity of the animal. After 4 to 5 minutes, the blood pressure returns to its initial level, at which time the unknown sample may be injected. If the rise produced is much greater or less than that of the standard solution, an amount or dilution which will give approximately the same rise is then injected.

CALCULATION OF THE AMOUNT OF HYPERTENSIN. After the tracing of blood pressure has been [illegible], the rise in pressure in mm. Hg produced by 1 unit of hypertensin and by the unknown solution is measured. The amount of hypertensin contained in this is calculated in units by the following formula: [illegible], where U represents units in unknown solution, a the rise in pressure in mm. Hg produced by the unknown, and b the rise in mm. Hg produced by the injection of 1 unit of standard solution of hypertensin. To avoid these calculations the nomogram reproduced in figure [illegible] may be used. In column 1 the rise of pressure produced by 1 unit of standard hypertensin is recorded and in column 4 that produced by the unknown. By uniting these points with a straight line, the amount in units is read at its intersection with the column line [illegible].

Example.—The injection of 1 unit of hypertensin into a dog produces a rise of 31 mm. Hg. [illegible] of the unknown sample produces an elevation of 121 mm. Hg. Since there is a considerable difference between the rises of pressure, [illegible] of the unknown sample is injected. This produces an elevation of 62 mm. Hg. The reinjection of 1 unit produces a rise of 28 mm. Hg. This rise produced by the standard solution is used in the calculation since it is the nearest to that produced by the unknown. Using the formula, [illegible] or 2.2 units in 0.5 cc. or 4.4 units in 1.0 cc. The same result is obtained by using the nomogram.

ASSAY OF HYPERTENSIN

PRINCIPLE OF THE METHOD *The rise of blood pressure* of an anesthetized dog produced by the intravenous injection of a solution of hypertensin of unknown strength *is compared with the rise of* pressure obtained with a standard solution of hypertensin of known potency.

TECHNIQUE. Due to their greater sensitivity, small dogs weighing 4 to 6 kgm are *preferably used. Chloralose was previously used as the* anesthetic. At the present time, nembutal or amytal (0 04 to 0 08 gm. of amytal per kgm ; 0 04 gm of nembutal per kgm.) are given by mouth or by intraperitoneal injection. The animals must be fasting Pithing under ether anesthesia followed by artificial respiration sometimes provides satisfactory preparations Once the dog is anesthetized the arterial and venous cannulas and the tracheal cannula are introduced by the usual technique. Artificial respiration must be so adjusted that it is sufficient but not excessive. It is advisable to maintain the pulmonary ventilation at the minimum necessary to preserve the normal color of the mucous membranes and yet sufficient to suppress spontaneous respiration of the animal. Cooling of the dog may be prevented by using a heated table. The blood pressure is recorded on a kymograph by the use of a suitable recording *manometer*

CRITERIA OF A GOOD PREPARATION. (a) *Sensitivity* —Sensitivity refers to the rise of pressure produced by a dose of hypertensin of known potency It varies from one animal to the next Generally speaking, 1 unit of standard hypertensin gives a rise varying between 20 and 60 mm Hg The greatest accuracy may be obtained when the animal is most sensitive If 1 unit of hypertensin produces a rise of less than 20 mm Hg, it is better not to use the animal

(b) *Constancy* —Since the sensitivity of the dog may vary from one moment *to the next, the sensitivity must be checked* repeatedly. A good preparation undergoes little change in sensitivity.

(c) *Regularity* —A good preparation shows no changes in heart rate, blood pressure or variations of blood *pressure from* respiratory causes

It is relatively easy *to fulfill the conditions* of constancy and regularity, especially if pithed preparations are used. As regards the

attainment of sensitive preparations, we can only suggest the use of small animals

Procedure.—The sample to be assayed is injected into the jugular vein If possible, the volume of injections should not exceed 10 cc. since large amounts may produce a pressor effect due to the volume injected After the injection, 5 cc of normal saline are drawn into the syringe and injected in order to wash the vein, since the position of the cannula prevents the circulation of blood through it

The regularity of the blood pressure tracing is checked. One unit of hypertensin is then injected in order to determine the sensitivity of the animal After 4 to 5 minutes, the blood pressure returns to its initial level, at which time the unknown sample may be injected If the rise obtained is much greater or less than that of the standard solution, an amount of standard which will give approximately the same rise is then injected

CALCULATION OF THE AMOUNT OF HYPERTENSIN. After the tracing of blood pressure has been suitably fixed, the rise of pressure in mm Hg produced by 1 unit of hypertensin and by the unknown solution is measured The amount of hypertensin contained in this is calculated in units by the following formula $U = (d/t)^2$, where U represents units of unknown solution, d the rise of pressure in mm Hg produced by the unknown, and t the rise in mm Hg produced by the injection of 1 unit of standard solution of hypertensin. To avoid these calculations, the nomogram reproduced in figure 92 may be used In column t, the rise in pressure produced by 1 unit of standard hypertensin is recorded and in column d, that produced by the unknown By joining these points with a straight line, the amount in units is read at its intersection with the oblique line, U.

Example.—The injection of 1 unit of hypertensin into a dog produces a rise of 30 mm Hg. Six cc of the unknown sample produce an elevation of 120 mm Hg Since there is a considerable difference between the rises of pressure, 0 5 cc. of the unknown sample is injected This produces an elevation of 42 mm Hg The re-injection of 1 unit produces a rise of 28 mm Hg This rise produced by the standard solution is used in the calculation since it is the nearest to that produced by the unknown Using the formula, $U = (42/28)^2$ or 2 2 units in 0 5 cc, or 4 4 units in 1 0 cc The same result is obtained by using the nomogram

The error of the determinations as we have just indicated depends particularly on the sensitivity of the dog and on its constancy. A certain amount of error is also introduced by assuming that in all animals the rises follow strictly the relation expressed by the formula employed. This source of error can be diminished by using an

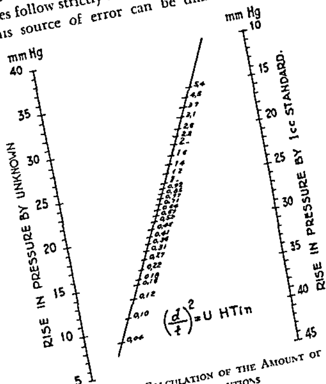


FIGURE 92 NOMOGRAM FOR CALCULATION OF THE AMOUNT OF HYPERTENSIN IN UNKNOWN SOLUTIONS

amount of hypertensin which gives approximately the same rise as that produced by the unit of standard hypertensin

If greater accuracy is necessary or desired, small amounts of hypertensin should be used Differences become more manifest when amounts under 1 unit are utilized. This may be done as follows. The amount of hypertensin in a given sample is calculated by the method just described An aliquot containing approximately 0.5 unit is taken. An amount of standard solution which produces a rise of pressure slightly less than that of the unknown is next injected. The unknown is then injected followed by a somewhat larger dose of the standard solution calculated to produce a slightly greater rise of pressure. In this way, the amount of hypertensin in the unknown lies somewhere

between two known amounts, one of which is greater and one of which is less

The calculation is based on the fact that with amounts of hypertensin which are approximately the same, the relation between rise of pressure and dose is linear as can be seen in figure 93. To make sure that the sensitivity of the assay animal has not changed, the rises of

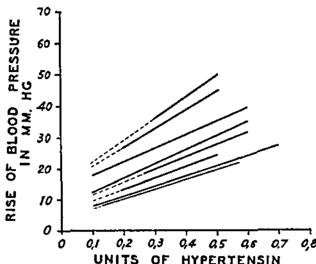


FIGURE 93 RELATION BETWEEN THE RISE OF BLOOD PRESSURE AND THE AMOUNT OF HYPERTENSIN

The lines represent results obtained in different dogs It is seen that within the limits indicated, the relation is linear, although there is some variation in the slope of the lines (After Taquini, Braun-Menéndez, Fasciolo, Leloir and Muñoz, Rev Soc. argent de biol, 1943, *19*, 500)

pressure obtained by the standard solution are plotted on a graph. If the slope of the line obtained by joining the points is similar to that in the graph of figure 93, the sensitivity may be considered to have remained constant, in which case the amount of hypertensin contained in the unknown solution can be estimated by simple extrapolation If the sensitivity has varied, the determination must be repeated

Example—A sample of hypertensin has already been found to contain approximately 1 unit in 2 cc, but a more precise assay is desired. Three-tenths cc of the standard solution is injected and a rise of 20 mm Hg pressure is obtained One cc of the unknown solution

The error of the determinations as we have just indicated depends particularly *on the sensitivity* of the dog and on its constancy. A certain amount of error is also introduced by assuming that in all animals the rises follow strictly the relation expressed by the formula employed. This source of error can be diminished by using an

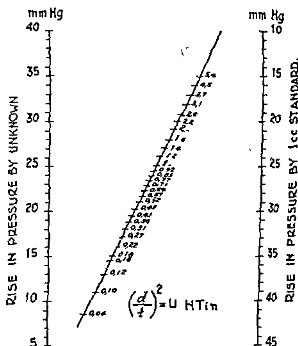


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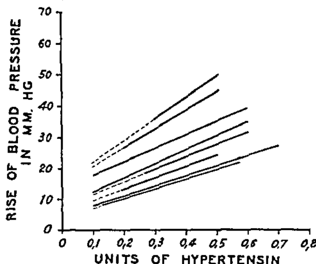


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Example—A sample of hypertensin has already been found to contain approximately 1 unit in 2 cc, but a more precise assay is desired Three tenths cc of the standard solution is injected and a rise of 20 mm Hg pressure is obtained, One cc of the unknown solution

produces a rise of 24 mm Hg, and 0.6 cc. of the standard gives a rise of 30 mm. Hg. By plotting on the graph the rises obtained with the known solution, it is observed that the slope of the line is approximately that which would be anticipated if there were no change in sensitivity. The rise of 24 mm Hg produced by the unknown is seen by extrapolation to correspond to 0.44 unit.

This method requires the use of extremely sensitive animals. Under satisfactory conditions, the error is not greater than 15 per cent.

METHOD OF ASSAY OF RENIN

DIRECT METHOD. *Principle.*—The amount of hypertensin formed by incubation of small amounts of renin with hypertensinogen in the absence of hypertensinase for 2 hours at 37°C. depends upon the concentration of renin.

Reagents—

(1) 2 M phosphoric acid
(2) Bromcresol green (0.1 per cent)
(3) 2 N and 0 5 N sodium hydroxide
(4) Phenol red
(5) Hypertensinogen without hypertensinase
(6) Merthiolate solution (Lilly) 1 per cent
(7) 0 5 M phosphate buffer pH 7.6

Procedure—(A) Collection of plasma: The sample of arterial or venous blood in which the presence of renin is to be investigated is collected in a centrifuge tube which contains 1 cc. of 3 8 per cent sodium citrate for each 10 cc of blood. The blood is centrifuged and the plasma placed in a test tube.

(B) Destruction of hypertensinase: The plasma is acidified with 2 M phosphoric acid, approximately 0 4 cc. being used for each 10 cc. of plasma The acid is added drop by drop with constant stirring until a yellowish-green color is obtained by mixing one drop of plasma with one drop of bromcresol green This corresponds to a pH of 4 2 according to the table of Clark. The first few drops of acid produce a turbidity of the plasma from precipitation of the proteins, but this turbidity disappears with further addition of acid. When the plasma recovers its transparency, it is in the neighborhood of the desired acidity The sample is then incubated at 37°C for 20 minutes In this way all of the hypertensinase and a large part of the hyperten-

sinogen are destroyed while the renin remains unaffected. The pH is then raised to 7.5 (phenol red) with 2 N sodium hydroxide added drop by drop with constant stirring

(C) Incubation of the samples with hypertensinogen: Different amounts of the above sample are placed in separate test tubes according to the amount of renin which may be expected to be present, for example, 2, 4, and 8 cc To each tube is added the following: (a) An amount of hypertensinase-free beef plasma (see preparation, page 353) which contains approximately 2 units of hypertensinogen. Six to 8 cc. are usually used (b) 0 3 cc of 1 per cent merthiolate solution (Lilly) (c) One cc of phosphate buffer pH 7.6, and (d) water *ad* 20 cc. The tubes are then incubated for 2 hours at 37°C. and the reaction stopped by pouring the contents of each tube into an Erlenmeyer flask containing 60 cc (3 volumes) of 96 per cent alcohol. Two control tubes are prepared The first contains the largest quantity of plasma employed in making up the previous tubes In the example above, this would be 8 cc The other reagents are added in exactly the same way as described, but the contents of the tube are precipitated with alcohol *without* previous incubation The second control tube contains an equal quantity of hypertensinase-free beef plasma (8 cc) and an amount of a known renin solution equivalent to 1 unit of renin After adding merthiolate and buffer, the tube is incubated for 2 hours as described

(D) Preparation of the samples to be injected· The samples are filtered by suction through Celite or Kieselguhr in Buchner filters and the alcoholic filtrate is concentrated under reduced pressure over boiling water to a volume of 2 to 3 cc The flask is washed with small amounts of distilled water, and this aqueous solution containing the hypertensin formed during the incubation is injected into a dog intravenously (see determination of hypertensin)

Calculation —One unit of renin is defined as that amount which produces 0 5 unit of hypertensin in 2 hours under the conditions described It is considered that the relation between the amount of renin present and amount of hypertensin formed is linear for values between 0 1 and 1 unit of hypertensin It is preferable to remain within this range since the assay of hypertensin is more accurate between these limits One-tenth unit of hypertensin formed corresponds to 0 2 unit of renin, 0 5 unit of hypertensin formed to 1 unit of renin, and so forth.

If the control tube gives a pressor response, as not infrequently happens, this amount, calculated in units of hypertensin, is subtracted from the amount found in the other tubes.

INDIRECT METHOD. *Principle.*—This method consists of measuring the amount of hypertensinogen before and after incubation with renin. The amount of hypertensinogen which is destroyed is proportional to the amount of renin present. Both human and pig renin act on beef hypertensinogen, but human hypertensinogen is not affected by pig renin. When a given amount of beef hypertensinogen is added to human plasma containing human renin, the amount of beef hypertensinogen remaining after incubation can be determined by adding an excess of pig renin which does not attack the human hypertensinogen

Reagents—

(1) Beef plasma
(2) 0.5 M phosphate buffer pH 7.3
(3) 1 per cent merthiolate solution (Lilly)
(4) Solution of hypertensinase

The solution of hypertensinase is obtained by hemolyzing 1 cc of fresh dog blood with 10 cc of distilled water.

Procedure—Three test tubes are made up as shown in the following table:

	Tube I (cc)	Tube II (cc)	Tube III (cc)
Sample of human serum	10	10	—
Beef plasma	2	—	2
0 5 M phosphate buffer pH 7 3	0 5	—	0 5
Merthiolate solution	0 6	0 3	0 3
Solution of hypertensinase	0 5	0 5	—

The 3 tubes are incubated at 37°C. for 6 hours Tubes II and III, which constitute the control tubes, are mixed at the end of this time. An excess of pig renin (3 cc. or 300 units) is added to tube I and the combined tube (II and III). Incubation at 37°C continues for 5 more minutes. The proteins are then precipitated by the addition of 3 volumes of 96 per cent alcohol. The solution is filtered, the filtrate

evaporated, the flask washed, and the amount of hypertensin present in the samples assayed in the dog by the method described.

The destruction of more than 0 40 unit of hypertensinogen indicates the presence of renin

If the amount of hypertensinogen destroyed is in the neighborhood of 0 90 unit, the serum contains 0 6 unit of renin. The destruction of 0 40 unit of hypertensinogen indicates the presence of 0.1 unit of renin The destruction of less than 0 40 unit should be interpreted with reservation since this approximates the limit of error of the assay of hypertensinogen.

PREPARATION OF HYPERTENSINASE-FREE HYPERTENSINOGEN

A solution of hypertensinogen of known strength and free from hypertensinase is used for the determination of renin

Principle —Hypertensinase in dog, beef and horse plasma may be totally destroyed with scarcely any effect upon the activity of hypertensinogen by subjecting it to a pH of 3 9 at 25°C. for 20 minutes Both hypertensinogen and hypertensinase in human plasma, however, are destroyed by this procedure

Reagents —

(1) 2 M phosphoric acid
(2) 0 1 per cent aqueous solution of bromcresol green
(3) 5 N sodium hydroxide
(4) 0 1 per cent aqueous solution of phenol red

PROCEDURE (A) *Collection of plasma* —Because of its availability in large amounts, we have used beef plasma for the preparation of hypertensinase-free hypertensinogen. Plasma from dogs and other animals, however, is entirely satisfactory The blood is either oxalated or defibrinated, precautions being taken to avoid hemolysis After centrifuging, the plasma or serum is saved One liter of plasma or serum is placed in a vessel with a capacity of two liters The container is thermostatically heated at 25°C until the temperature of the plasma or serum comes into equilibrium

(B) *Destruction of hypertensinase* —Phosphoric acid is added drop by drop with constant stirring with a glass rod until 1 drop of the plasma mixed with 1 drop of bromcresol green gives a yellowish-green

color corresponding to a pH of 4.2 according to the table of Clark. Electrometric determinations have shown that this color corresponds to a pH of 3.9. Approximately 40 cc. of phosphoric acid are necessary for the proper acidification of 1 liter of plasma or serum.

The solution is incubated at 25°C. for 20 minutes Sodium hydroxide is then added drop by drop with constant stirring, until 1 drop of the plasma mixed with 1 drop of phenol red gives a rose color corresponding to a pH of 7.4 according to the table of Clark Approximately 16 cc. of 5 N sodium hydroxide are required for this step.

(C) *Testing of the plasma*.—Before using this plasma for the assay of renin, it is advantageous to ascertain (1) if all of the hypertensinase has been destroyed, (2) if it contains hypertensinogen activity, and (3) if the alcoholic extract of this plasma possesses a pressor or depressor effect on being injected intravenously into a dog.

The following tests are therefore carried out. (1) In order to be sure of the complete destruction of hypertensinase, 8 cc of the treated plasma are incubated for 2 hours at 37°C. with 1 unit of hypertensin, buffer and Merthiolate being added according to the method described on page 355 An unincubated control tube is made with the same mixture. The pressor action of the alcoholic extracts of both tubes should be the same. (2) The amount of hypertensinogen contained in the beef plasma after destruction of the hypertensinase is determined according to the method described at foot of page. About 1 unit is usually present in each 3 to 4 cc. of the hypertensinase-free plasma (3) An alcohol extract of 15 to 20 cc. of treated beef plasma incubated for 2 hours at 37°C is tested for its action on the blood pressure of the dog. If the pressor or depressor action is extreme, the preparation is discarded.

(D) *Storage*.—A small amount of toluol (5 to 10 cc.) is added to the hypertensinase-free beef plasma thus obtained, and it should be stored in the ice box in a closed vessel Its potency remains unchanged for months. If a precipitate appears after some time, it can be removed by filtration or centrifugation.

METHOD OF ASSAY OF HYPERTENSINOGEN

Two cc of plasma are added to 0 5 cc of 0 5 M phosphate buffer at pH 7 4 The mixture is heated in a water bath at 37° to 40°C. for 5 minutes. In the case of human hypertensinogen, 2 to 3 cc. of

hypertensinase-free human renin containing not less than 50 units per cc. are added In the case of dog or rat hypertensinogen, 2 to 3 cc. of hypertensinase-free pig renin containing about 100 units per cc. are added. The mixture is incubated at 37°C. for 7 minutes. At the end of this time it is removed from the water bath Enough saline solution is added to bring it to a volume of 10 cc and the proteins are precipitated by adding 30 cc of 96 per cent alcohol This is then filtered.

The hypertensin formed remains in the filtrate. The alcohol and water are removed by evaporation under reduced pressure over boiling water The pressor effect is recorded in the assay animal, the hypertensin present being calculated according to the method described above The amount of hypertensin contained in 1 cc of the mixture of plasma and citrate is calculated Correction for dilution with citrate is made Assays should be carried out in duplicate. If differences are greater than 30 per cent, the assays should obviously be discarded.

METHOD OF ASSAY OF HYPERTENSINASE

To a series of test tubes, 10 cc of the following mixture are added·

Hypertensin	10 units
0.5 M phosphate buffer pH 7 4	5 cc
Merthiolate (Lilly) 1 per cent	2 cc
Water *ad*	100 cc

Graded amounts of the unknown hypertensinase solution are added to the different tubes The volume of hypertensinase solution should not exceed 0 5 cc One of the tubes, to which hypertensinase is not added, serves as a control Each tube is incubated for 4 hours at 37°C The tubes are then placed in a boiling water bath for 5 to 10 minutes. The amount of hypertensin remaining in the tubes is assayed in the dog by the method described One unit of hypertensinase is defined as the amount which destroys 0.5 unit of hypertensin in 4 hours of incubation under the conditions described In case exactly 0.5 unit of hypertensin is not destroyed in any one of the tubes, the amount present may be estimated by consulting the curve shown in figure 68, page 170

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